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Litman's Basics of Pediatric Anesthesia

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Litman's Basics of Pediatric Anesthesia

Third Edition

Ronald S. Litman, DO, ML

Professor of Anesthesiology and Critical Care Medicine, Pediatrics
Children's Hospital of Philadelphia
Perelman School of Medicine at the University of Pennsylvania

Aditee P. Ambardekar, MD, MSEd

Residency Program Director
Associate Professor and Distinguished Teaching Professor
Department of Anesthesiology and Pain Management
Children's Health, Dallas
UT Southwestern Medical Center

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Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
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In Memoriam

This edition of Litman's Basics of Pediatric Anesthesia *honors the physician, mentor, colleague, and friend that Dr. Litman was to many of us. His curiosity of all things medical and nonmedical, his inclination to challenge all things status quo, and his enduring commitment to training and mentoring the next generation of pediatric anesthesiologists defined his professional and personal life. So many colleagues benefited from his sponsorship, myself included, as evidenced by my coeditorship of this book. May Dr. Litman's enthusiasm for pediatric anesthesia and support for our learners live on in readers of this book for years to come.*

List of Contributors

Adam C. Adler, MD, MS, FAAP, FASE
Associate Professor
Department of Anesthesiology, Perioperative and Pain Medicine
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

Aditee P. Ambardekar, MD, MSEd
Associate Professor and Distinguished Teaching Professor
Department of Anesthesiology and Pain Management
UT Southwestern Medical Center and Children's Health
Dallas, TX

Naomi Balamuth, MD
Associate Professor of Clinical Pediatrics
Department of Pediatrics
Division of Oncology
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Alexandra Berman, MD
Resident
Department of Anesthesiology
New York Presbyterian Weill Cornell Medicine
New York, NY

Tarun Bhalla, MD, MBA, FASA, FAAP
Chair
Department of Anesthesiology and Pain Medicine
Akron Children's Hospital
Professor
Anesthesiology and Surgery
Northeastern Ohio Medical University (NEOMED)
Akron, OH

Donald L. Boyer, MD, MSEd
Associate Professor of Clinical Anesthesiology and Critical Care
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
Division of Critical Care Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Andrew J. Costandi, MD, MMM
Clinical Associate Professor of Anesthesiology
Department of Anesthesiology Critical Care Medicine
Division of Pain Management
Keck School of Medicine of USC
Children's Hospital of Los Angeles
Los Angeles, CA

C. Hunter Daigle, MD
Assistant Professor
Department of Pediatrics
Division of Critical Care Medicine
The University of Texas at Austin
Dell Medical School
Dell Children's Medical Center
Austin, TX

Gregory Dodson, DO
Assistant Professor
Department of Anesthesiology
Cooper Medical School of Rowan University
Camden, NJ

Jeffrey M. Feldman, MD, MSE
Professor of Anesthesiology and Critical Care
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

John E. Fiadjoe, MD
Assistant Professor of Anesthesiology
Harvard Medical School
Boston Children's Hospital
Boston, MA

Jessica Foster, MD
Instructor and Attending Physician
Department of Pediatrics
Division of Oncology
Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Susan Gallagher, RN
Hemophilia Nurse Coordinator
Children's Hospital of Philadelphia
University of Pennsylvania
Philadelphia, PA

F. Jay Garcia, MD
Resident
Department of Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Thierry Girard, MD
Deputy Chair
Anesthesiology
University Hospital Basel
Switzerland

Anastasia D. Grivoyannis, MD
Assistant Professor
Department of Anesthesiology & Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, MD

Harshad Gurnaney, MBBS, MPH
Associate Professor of Anesthesiology and Critical Care
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Fatimah Habib, MD
Assistant Professor of Anesthesiology
Assistant Professor
Department of Anesthesiology
Cooper Medical School of Rowan University
Camden, NJ

Grace Hsu, MD
Clinical Associate Professor of Anesthesiology
Department of Anesthesiology Critical Care Medicine
Division of Pain Management
Keck School of Medicine of USC
Children's Hospital of Los Angeles
Los Angeles, CA

Samuel Hunter, MD
Assistant Professor of Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Rebecca S. Isserman, MD
Assistant Professor of Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Jeremy Jones, MD
Resident
Department of Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Ji Yeon Jemma Kang, MD
Assistant Professor
Department of Anesthesia
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Michael R. King, MD
Assistant Professor
Northwestern University Feinberg School of Medicine
Ann and Robert H. Lurie Children's Hospital of Chicago
Chicago, IL

F. Wickam Kraemer III, MD
Associate Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Grace E. Linder, MD
Assistant Professor
Department of Pathology and Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Ronald S. Litman, DO, ML
Professor of Anesthesiology and Critical Care Medicine and Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Katherine H. Loh, MD
Assistant Professor
Department of Anesthesiology
Division of Pediatric Anesthesiology
Vanderbilt School of Medicine
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, TN

Petar Mamula, MD
Professor of Pediatrics
Department of Pediatrics
Division of Gastroenterology, Hepatology, and Nutrition
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Annery Garcia-Marcinikiewicz, MD
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Lynne G. Maxwell, MD
Emeritus Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Wallis T. Muhly, MD
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Olivia Nelson, MD
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Asha Nookala, MD
Pediatric Anesthesiologist
Children's Minnesota
Minneapolis, MN

Vanessa A. Olbrecht, MD, MBA, FASA
Associate Professor
Department of Anesthesiology and Pain Medicine
Nationwide Children's Hospital
Columbus, OH

Shikha Patel, BS
Medical Student
Drexel University College of Medicine
Philadelphia, PA

Alison Perate, MD
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Laura A. Petrini, MD
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Teeda Pinyavat, MD
Assistant Professor
Department of Anesthesiology
Division of Pediatric Anesthesiology
Columbia University
New York, NY

Andrew Renuart, MD, MSc
Assistant in Perioperative and Critical Care Medicine
Department of Anesthesiology
Critical Care and Pain Medicine
Boston Children's Hospital
Instructor of Anaesthesia
Harvard Medical School
Boston, MA

Susan R. Rheingold, MD
Professor of Clinical Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Samuel Rosenblatt, MD, MSEd
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Julia Rosenbloom, MD
Assistant Professor
Mass General Anesthesia and Pain Medicine
Boston, MA

William Ryan, BS
Medical student
Drexel University College of Medicine
Philadelphia, PA

Deborah Ann Sesok-Pizzini, MD, MBA
Chief, Blood Bank and Transfusion Medicine
Pathology and Laboratory Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Christopher Setiawan, MD
Assistant Professor
Department of Anesthesiology and Pain Management
UT Southwestern Medical Center and Children's Health
Dallas, TX

Allan F. Simpao, MD, MBI
Associate Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Paul A. Stricker, MD
Associate Professor of Clinical Anesthesiology and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Ari Y. Weintraub, MD
The Perelman School of Medicine at the University of Pennsylvania
Department of Anesthesiology and Critical Care
Children's Hospital of Philadelphia
Philadelphia, PA

Char M. Witmer, MD, MSCE
Associate Professor of Clinical Pediatrics
Department of Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Theoklis Zaoutis, MD, MSCE
Professor of Pediatrics and Epidemiology
Division of Infectious Diseases
The Perelman School of Medicine at the University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Karen B. Zur, MD
Professor and Chief
Division of Otolaryngology
Department of Otolaryngology
Head and Neck Surgery
The Perelman School of Medicine at The University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Preface

When I sat down to write the preface of this book, I spent a fair bit of time wondering, "What was Ron thinking?" Not in a critical way; rather, I wondered how I could best represent the thoughts and energy that Ron put into this without the pleasure of having a colorful conversation with him. Although I had very little role in assembling the content and authors, I felt a huge responsibility for completing this in the way Ron had intended, ultimately to honor his work. In the best way I knew how, I hobbled together something based on past prefaces, my review of the book in its entirety, and my knowledge of Ron. Well, Ron must not have been thrilled with the way it sounded because, as we were preparing the book for copyediting, he made sure we found the file of the preface he intended for this edition of the book. What a treat to hear his voice in the words on this page. Enjoy!

Aditee P. Ambardekar, MD, MSEd

I caved. After a very successful run self-publishing *Basics of Pediatric Anesthesia* in 2013, I didn't have the energy to self-publish again. It takes a lot of work and focus worrying about the cover, layout, tables, photos, and figures. And that godawful index! Then there's the marketing, distribution, author-chasing, and wondering who, if anyone, will ever buy it after all that effort. So, in 2020, when I knew that some of the concepts in *Basics* were getting seriously out of date, I caved. I sent book proposals to publishers of anesthesia textbooks and was lucky enough to connect with Sarah Barth of Elsevier, who, along with Ellen Wurm-Cutter, stewarded this next edition through to completion. So, there are a few less jokes. It was time to grow up anyway.

Many aspects of the practice of clinical pediatric anesthesia that have changed since the first edition are now addressed in this third edition. They include opioid sparing, sugammadex, changes in fasting intervals, difficult intubation protocols, and pediatric advanced life support algorithms, to name just a few. Don't worry: anesthesia circuits are still absent. I'm sticking with the basics. Many of the original chapter authors have been replaced with motivated and energetic junior pediatric anesthesiologists (and sometimes even brilliant medical students) to fact-check the chapters and add additional material where appropriate.

One new aspect of *Basics* is the inclusion of special sections called "Deeper Dive," designed for readers that want a more nuanced and granular perspective on a particular topic. Most of these Deeper Dives consist of detailed examination of published research studies that have not only advanced knowledge in pediatric anesthesia but have also influenced its practice. These sections are scattered throughout the book. Some chapters have none, while some have more than one.

Notably absent from this revision is any mention of the anesthetic management of children with SARS COVID-19. As I write this, we are in the midst of two of the worst public health crises in US history, notably, the viral pandemic and continuing racial injustice. Fortunately, I am confident that by the time *Basics* is published, we will have emerged from the pandemic with many lessons learned about the public health implications of the management of children with severe viral disease or the cytokine storm that follows. There is no doubt that dangerous pandemics will recur in most of our lifetimes, but this material is not suitable in a book on the basics.

Unfortunately, I am not confident that racial injustice will be similarly relegated to the past. That's why I've asked Julia Rosenbloom, a pediatric anesthesiologist, to write a section on racial inequities in pediatric anesthesia and pain management. Julia is currently on the faculty of Harvard Medical School and has devoted her career to this crucially important topic. Every anesthesia provider should be intimately familiar with our unacceptable track record of treating children of color and how to advocate for and protect those children and their families.

Ronald S. Litman, DO, ML

Acknowledgements

Editorship of this edition fell into my lap in April 2021 under extenuating circumstances as Ron spent some of his last moments with his sweet family. Ron had spent the better part of 2020 planning his third edition, recruiting young authors to update the content, and editing the chapters as they came in... all the while fighting cancer and getting stronger. What had been a small commitment from me in November 2020 to update the pediatric burn chapter morphed into one of the biggest honors of my professional career. Ron and Daphne, thank you for the opportunity to honor Ron's legacy in pediatric anesthesia as the coeditor of this book.

It would have been ideal to have done this alongside Ron, as had originally been planned down the road, rather than in his absence. However, this was not meant to be. Through Ron's sponsorship and the mentorship of several individuals, however, I felt empowered to take the baton and cross the finish line. To Ron and the many others who served and continue to serve in a role of mentor to me, I thank you. I hope I can be as impactful of a mentor to others as you have been to me. You know who you are.

All of this is for naught without the medical students, residents, and fellows we have the honor and responsibility to teach. It is your inquisitiveness, compassion, and dedication to our field that energizes those of us in academic medicine. Thank you for the privilege to be part of this exciting journey.

Finally deepest gratitude to my family. To my mother and father, who instilled in me the desire to work hard and make a difference with humility and grace, I thank you. As Dr. Schwartz would say, I "picked the right parents." To my husband, Sumeet, who believes in me and encourages me with any new academic endeavor, I thank you. Your support means the world to me. To my sons, Arjun and Aarav, thank you for sharing your mommy with her patients, her residents and fellows, and her work. Although some days feel like cacophony rather than harmony, your unconditional love and beautiful souls make it all worth it.

Aditee P. Ambardekar, MD, MSEd

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Litman's Basics of Pediatric Anesthesia

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1 Transition From Fetal to Pediatric Anesthesia

VANESSA OLBRECHT, ANDREW RENUART AND RONALD S. LITMAN

We begin this journey into the magical world of pediatric anesthesia by describing fetal cardiopulmonary physiology and the physiologic changes that occur during birth. Knowledge of these changes is important for understanding the pathophysiologic conditions that occur in neonates when these changes do not occur normally.

First, for clarity and consistency across the pediatric anesthesia literature, and to make sure we are all on the same page, there are a few universal definitions that you need to know.

- A ***neonate*** is a child in the first 28 days (or 1 month) of life, regardless of gestational age.
- An ***infant*** is a child from birth to 12 months of life.
- The ***gestational age*** is the number of weeks between conception and birth.

The following definitions are relatively new[1]:

- ***Early term*** delivery refers to birth during the period between 37 and 38 6/7 weeks' gestation.
  - ***Full term*** refers to delivery between 39 and 40 6/7 weeks' gestation.
- ***Late term*** refers to delivery between 41 and 41 6/7 weeks' gestation.
  - ***Postterm*** refers to delivery after 42 weeks' gestation.
- ***Extremely preterm*** infants are born before 28 weeks' gestation.
- ***Very preterm*** infants are born between 28 and 31 6/7 weeks' gestation.
- ***Moderate to late preterm*** infants are born between 32 and 36 6/7 weeks' gestation.

Sometimes, newborn infants are classified by their weight relative to their gestational age. For example:

- ***Appropriate for gestational age (AGA)*** describes an infant with a birth weight between the 10th and 90th percentiles.
- ***Small for gestational age (SGA)*** describes an infant with a birth weight below the 10th percentile.
- ***Large for gestational age (LGA)*** describes an infant with a birth weight above the 90th percentile.

Intrauterine growth restriction (IUGR) is an abnormal pattern of restricted fetal growth for gestational age. It is mainly an obstetric term that is used to describe a pattern of growth over a period of time *in utero*, whereas *SGA* is a term used by pediatricians to describe the infant at or shortly after birth.

Lung Growth and Development

During gestation, the fetal lungs grow and develop but are not responsible for oxygenation and ventilation. We normally rely on the lungs to provide oxygenation and ventilation, but in fetal life, that is the placenta's responsibility. The intrauterine environment allows the alveoli and bronchial tree of the lungs to develop. The fetal lungs are filled with fluid and transition to their role as the organ of gas exchange shortly before, during, and after the birth process.

Fetal lung development is divided into four stages of progressive lower airway and alveolar growth (Table 1.1). In the embryonic stage, primitive lung tissue is developed and vascular connections are made. In the pseudoglandular stage, the bronchial tree begins to form lumens, and in the canalicular stage at 16 to 26 weeks' gestation, alveoli begin to form. It is also during this period that blood and lymphatic vessels begin to develop in parallel to the bronchial tree, and surfactant production begins. Finally, during the saccular stage, the fetal lung completes the physiologic processes that allow it to accomplish respiration in the extrauterine environment. This includes maturation of the alveolar-vascular interface and development of a full complement of surfactant, which will reduce surface tension within the alveoli and prevent their collapse after transition to the outside world. During gestation, the fetal airways and alveoli become distended by secreted lung fluid, which becomes a component of the amniotic fluid and allows for proper development of the lungs.

As the peripheral chemoreceptors and the respiratory center of the brain mature, the fetus develops stronger and more

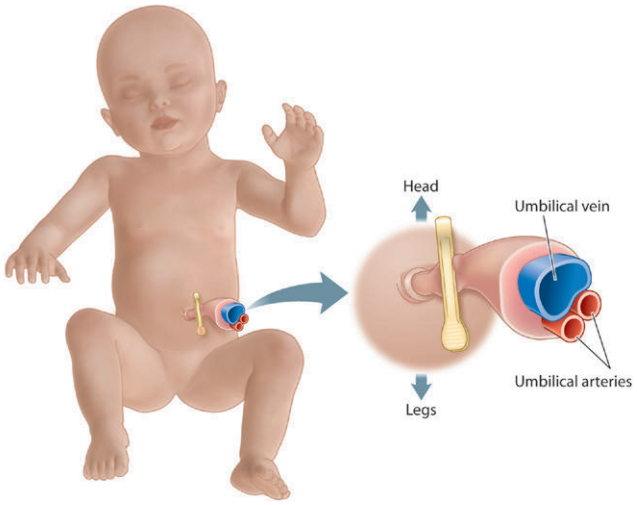
TABLE 1.1 Stages of Fetal Lung Development

Stage	Gestation	Events
Embryonic	4–17 weeks	Formation of primitive lung tissue and vascular connections.
Pseudoglandular	5–17 weeks	Development of a bronchial tree that begins to form lumens.
Canalicular	16–26 weeks	Alveoli begin to form. Vascular and lymphatic systems develop alongside the bronchial tree. Differentiation of type 1 and type 2 pneumocytes with beginning of surfactant production. Extrauterine life possible at later weeks.
Saccular	24 weeks–birth	Peripheral bronchiole branching. Maturation of surfactant system. Breathing efforts begin. 30–50 million alveoli at birth.
Alveolar	Birth–3+ years	Continued alveolar growth to adult level of approximately 500 million. Reduction of interstitial tissues.

regular breathing patterns throughout development. After the 30th week of gestation, the fetus is seen to "practice" breathing at about 60 times per minute, approximately 40% of the time. There are conflicting reports as to the number of years into childhood that it takes for the alveoli to finish growing. In the past, it was thought that alveolar growth terminated somewhere between 3 and 8 years; but more recent data indicate that it could be even later into childhood.

Development of the Circulatory System

The primary difference between the fetal and adult circulatory systems is that the fetal circulation consists of two parallel circulations (right and left), whereas the adult system exists in series. Fetal circulation is also characterized by the presence of several right-to-left shunts that result from the high pulmonary vascular resistance of the fetal lungs and the low vascular resistance of the placenta. The main purpose of having a fetal circulation is to distribute oxygen, glucose, and



• **Fig 1.1.** Umbilical cord anatomy. *(Illustration by Rob Fedirko.)*

other nutrients from the placenta (which receives about 40% of mom's cardiac output) to the developing brain and vital organs of the fetus.

Let us describe the pattern of fetal circulation by starting with blood returning to the placenta. Deoxygenated blood from the fetus travels to the placenta via the two umbilical arteries that are encased by the umbilical cord (Fig. 1.1). In the placenta, the fetal blood picks up oxygen, releases carbon dioxide, and is returned to the fetus via the single umbilical vein (also contained in the umbilical cord). With a PO_2 that may reach as high as 55 mm Hg, fetal blood is at its highest oxygen level in the umbilical vein. This may seem low compared with the developed human, but there are several reasons why the fetus is able to successfully maintain adequate tissue oxygenation with such a low PO_2. These include:

- Fetal hemoglobin (Hgb F) has a higher affinity for oxygen than maternal hemoglobin, which facilitates movement of oxygen from the maternal to the fetal blood via diffusion. This increased affinity of Hgb F for oxygen causes a leftward shift of the oxyhemoglobin dissociation curve.
- Release of oxygen from Hgb F to fetal tissues is facilitated by the relatively higher temperature and lower pH of the fetus, both of which shift the oxyhemoglobin dissociation curve to the right.
- A relatively low PO_2 is better suited to the metabolic needs of the fetus, which has relatively lower oxygen consumption.
- Evolutionary forces influenced the fetal circulation such that blood flow with a relatively higher degree of oxygen saturation preferentially perfuses vital organs such as the liver, heart, and brain.

Oxygenated blood is carried through the umbilical vein to the liver, where approximately half of the blood flow joins the hepatic circulation to supply oxygen and nutrients to the hepatic tissue, while the other half bypasses the liver through the ***ductus venosus***, a structure present only in fetal life. The ductus venosus carries the oxygenated blood

into the inferior vena cava (IVC). Here, the oxygen-rich blood mixes with poorly oxygenated blood returning from the fetal lower extremities and the newly acquainted circulations travel together to the right atrium.

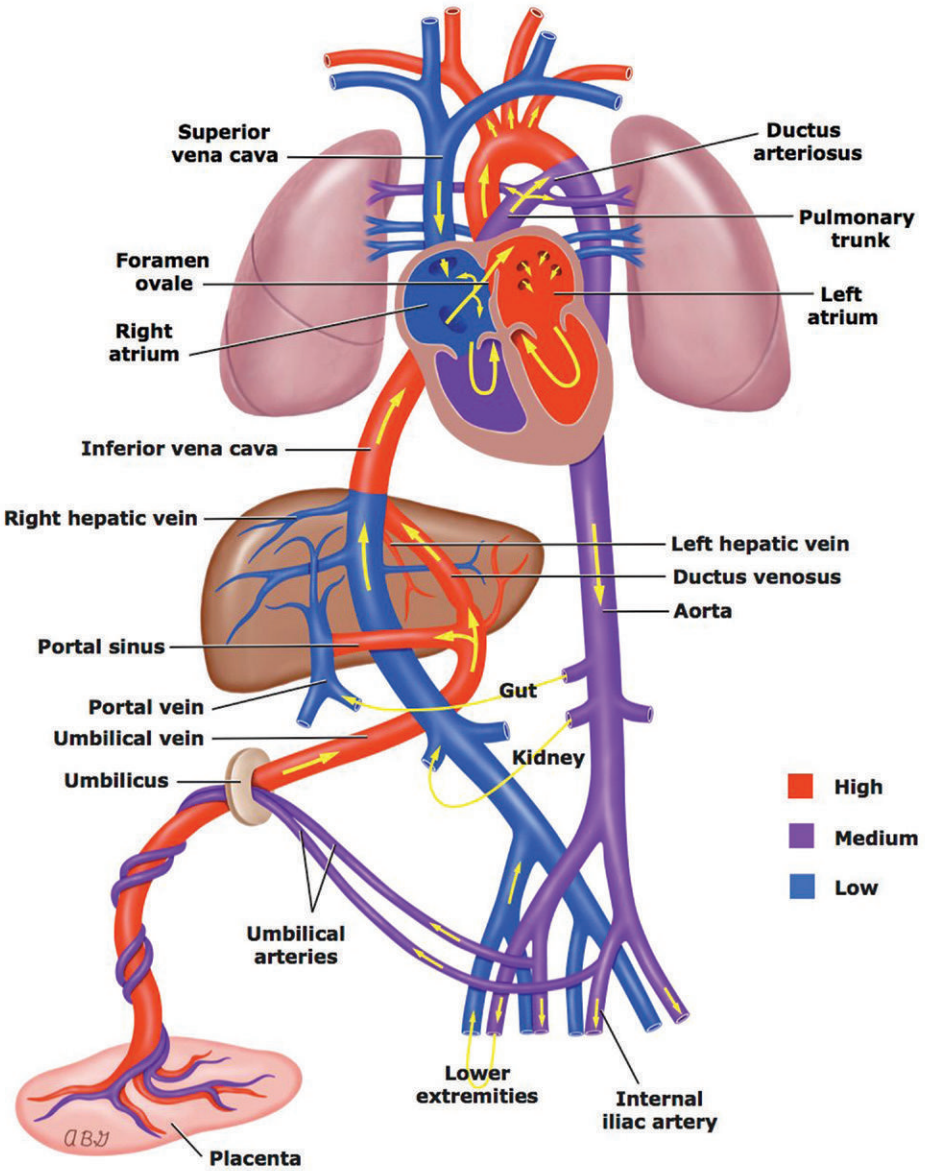
Inside the fetal right atrium, oxygenated blood from the IVC is preferentially directed across the ***foramen ovale*** and into the left atrium, while deoxygenated blood returning from the head via the superior vena cava (SVC) is preferentially directed to the tricuspid valve into the right ventricle. This circulation pattern allows preferential perfusion of oxygen-rich blood to vital organs.

The deoxygenated blood that enters the right ventricle is ejected into the pulmonary artery, but because pulmonary vascular resistance is high, only a small portion (about 10%) actually gets into the pulmonary arterial system. Most (90%) is directed through the ***ductus arteriosus***, a connection between the pulmonary artery and the aorta, where it joins aortic blood flow returning to the placenta via the umbilical arteries. The ductus arteriosus usually enters the aorta just distal to the origin of the left subclavian artery.

The oxygenated blood that has crossed into the left atrium passes through the mitral valve into the left ventricle and is ejected out through the ascending aorta where it provides oxygen and glucose to the developing brain via the carotid arteries. Although the PO_2 is now about 27 mm Hg, the fetus still receives sufficient oxygen for fetal organ growth.

Cardiopulmonary Changes at Birth

The birth process entails several complicated physiologic transitions to an extrauterine existence that all seem to occur at once (Fig. 1.2). Alveolar and bronchial fluid must be



• **Fig 1.2.** Fetal circulation. (Reproduced with permission from: Fernandes CJ. Physiologic transition from intrauterine to extrauterine life. In: Post TW, ed., *UpToDate* (website). Accessed on 20.9.22. Available from: www.uptodate.com.)

expunged, the lungs must expand, and the circulatory conduits that serve as right-to-left shunts must quickly close. When these occur, the lungs officially become the organ of respiration and the cardiovascular system converts from two parallel circulations to two circulations in series. If any of these fails to occur, hypoxemia may result from residual right-to-left shunting.

Several mechanisms facilitate the clearance of alveolar fluid from the fetal lungs. During labor, a state of physiologic stress that is induced in the fetus causes the lung epithelium to convert from one that secretes liquid into the air spaces to one that actively reabsorbs salt and fluid. This change is further enhanced when the lung epithelium is exposed to oxygen after delivery. During the newborn's first breaths, air is drawn into the lungs because of a large negative inspiratory force, and lung fluid is absorbed or expelled. Intrathoracic pressures are estimated to range from -60 cmH_2O during inhalation and approximately $+70$ cmH_2O during exhalation. This large fluctuation in intrathoracic pressure helps force fluid from the air spaces into the interstitium and then ultimately back into the intravascular space. The pressure required for lung expansion becomes increasingly less negative over several breaths. These initial breaths establish the residual volume (RV) and functional residual capacity (FRC) of the newborn's lungs. These volumes are maintained by the newborn's expiratory braking maneuver (see Chapter 2) that also prevents the expunged fluid from reentering the lungs. Pressure exerted on the chest from contractions during delivery is thought to play only a minor role in this transition.

Also important in this transition is the shift in vascular resistance that occurs when the umbilical cord is clamped as the newborn takes its first breaths. Clamping the umbilical cord causes a dramatic increase in systemic vascular resistance (SVR) and immediate loss of preload from the umbilical vein. At the same time, as the lungs expand, the increase in pulmonary PO_2 causes pulmonary vascular resistance (PVR) to decrease; pulmonary blood flow increases and reestablishes preload to the left ventricle. Arterial blood gas values normalize within the first 24 hours of life.

The combined increase in SVR and decrease in PVR cause resistance to blood flow through the ductus arteriosus. Increasing left atrial pressure causes the "flap-valve" foramen ovale (which connects the right and left atria) to close, thus establishing for the first time a circulation in series. The umbilical arteries form a portion of the internal iliac and superior vesical arteries, and the ductus venosus (previously supplied by the umbilical vein) will atrophy and form a remnant known as the ***ligamentum venosum***.

Over the first several hours of life, the ductus arteriosus functionally closes as a result of constriction of specialized contractile tissue within its arterial wall. This constriction is caused by a number of factors, including withdrawal from placenta-derived prostaglandin E2, an increase in arterial oxygen tension, and an increase in blood pH. Over the next several weeks, the ductus arteriosus becomes anatomically closed; its remnant is called the ***ligamentum arteriosum***.

Persistent Pulmonary Hypertension of the Newborn

Although the majority of neonates undergo this transition to extrauterine life successfully, approximately 10% will have difficulty and will require some level of neonatal resuscitation. Several factors are associated with an increased risk of requiring assistance. These include maternal conditions (e.g., advanced maternal age, maternal substance abuse), fetal conditions (e.g., prematurity, congenital anomalies), and delivery complications (e.g., breech presentation, peripartum infection). Any of these could result in hypoxia, hypercarbia, and/or acidosis, all of which predispose to the newborn's inability to transition out of fetal circulation.

A particularly hazardous outcome from this transition failure is the development of **persistent pulmonary hypertension of the newborn (PPHN).** This disorder leads to persistence of pulmonary vasoconstriction, which causes pulmonary hypertension. PPHN primarily occurs in term or late preterm infants over the age of 34 weeks' gestation, and its prevalence is estimated to occur in approximately 2 per 1000 live births.

Because of the abnormally high PVR, the fetal pattern of circulation continues: blood flows through a patent ductus arteriosus (PDA) or foramen ovale in a right-to-left direction and hypoxemia worsens, thus creating a vicious cycle that can be overcome only by aggressive therapy for the underlying disorder and reversal of hypoxemia, hypercarbia, and acidosis. The management of PPHN focuses on supportive measures, including the use of 100% oxygen, with the goal of decreasing PVR compared with SVR. Other more aggressive treatment measures include the use of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO).

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2

Developmental Physiology and Pharmacology

SHIKHA PATEL AND RONALD S. LITMAN

Developmental physiology describes the bodily changes that take place during early development. Anesthesiologists must be familiar with these changes as they pertain to the different organ systems. Developmental pharmacology describes the changes in pharmacokinetics and pharmacodynamics during early life. In pediatric anesthesia, this is especially important because it influences the administration of intravenous and inhaled anesthetic agents in young children.

Respiratory Physiology

A term newborn will have near full functionality of the lungs within several hours after birth. Its lung contains approximately 50 million alveoli, which grow during early childhood until reaching the adult level of approximately 500 million sometime before adolescence.

Healthy term newborns have a well-developed biochemical and reflex control of ventilation. Although they may demonstrate episodes of periodic breathing that last 5 seconds or more, in the healthy infant, these episodes of central apnea are self-limited and are not associated with clinically significant bradycardia, which may occur in preterm infants. Periodic breathing after the first month of life is not normal and should warrant further investigation.

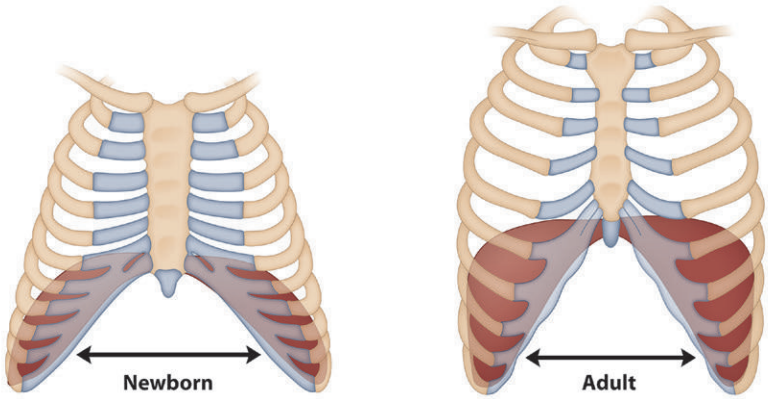
One of the ways that respiratory physiologists measure ventilatory drive is to note the increase in ventilation when a subject inhales carbon dioxide (CO_2). The newborn's ventilatory response to breathing CO_2 will be less than that of older children. The newborn's response to breathing a hypoxic mixture is more unique and includes an immediate increase in ventilation that lasts about 1 minute, followed by a decrease in ventilation that lasts about 5 minutes. This reflects carotid body immaturity, and differs from older children in whom the initial protective phase of ventilatory stimulation has a longer duration. This shortened phase of ventilatory depression is even more prominent during hypercarbia, acidosis, or hypothermia.

Newborns demonstrate maladaptive respiratory depression (including apnea) in response to certain provocations that would normally result in stimulation of respiratory function in older infants. These stimuli may include lung inflation (Hering-Breuer reflex), stimulation of the carina or superior laryngeal nerve, and upper airway obstruction. Taken together, all these observations demonstrate the relatively weaker ability of newborns to adapt to acute hypoxemia.

The most important differences in respiratory function between children and adults are anatomically based, related to the growth and maturity of the chest wall during the first 2 years of life. These differences directly influence the mechanism by which functional residual capacity (FRC) is maintained. The newborn infant's FRC is established in the first several breaths after birth. In unanesthetized infants and adults, FRC is approximately the same, although the mechanisms by which FRC is attained are different in these two populations. However, when anesthetized, these differences impart substantial effects on FRC.

In neonates and small infants, the orientation of the ribs is more parallel than angled (Fig. 2.1). This results in a relative inefficiency of movement because the volume of the rib cage is not increased by raising the ribs as in older children and adults. At about 2 years of age, when the child spends more time in the upright position, the effect of gravity causes the ribs to be angled downward, and the rib cage then becomes more adult-like, thus providing an advantage to maintaining FRC while anesthetized. During early childhood development, the structure of the ribs becomes bonier and less cartilaginous and provides an inherent stiffness to the thoracic cavity. This stiffness imparts a tendency for the chest wall to expand outward, which counteracts the tendency for the lungs to collapse inward. The opposing tendencies between lungs and chest wall generate a slightly negative intrapleural pressure at the end of exhalation, and serve to maintain FRC in older children and adults, but this mechanism does not exist in infants.

The chest wall of neonates and small infants is primarily cartilaginous because it has not yet developed its bony components. It is highly compliant and tends to collapse



• **Fig 2.1** Developmental changes of the rib cage and diaphragm from birth to adulthood. Adults can increase lung volume by raising the ribs and contracting the diaphragm. Early in development, the configuration of the rib cage and muscular attachments of the diaphragm place the newborn at a mechanical disadvantage because the ribs are already "raised," and contraction of the diaphragm results in a relatively smaller increase in thoracic cavity volume. (Illustration by Rob Fedirko.)

inward along with the lungs. As a consequence, infants must maintain their negative intrathoracic pressure (and negative intrapleural pressure) by active recruitment of accessory muscles of respiration, such as the intercostal muscles. In addition, the adductor muscles of the larynx of the neonate act as a valve; they contract during exhalation to maintain positive end-expiratory pressure and contribute to the maintenance of FRC. This phenomenon is called *laryngeal braking*. Newborns commonly demonstrate prominent abdominal excursions during normal breathing because of their reliance on diaphragmatic contraction for development of a sufficiently negative intrapleural pressure during inspiration. Despite the above-mentioned intrinsic mechanisms that attempt to maintain lung volumes, neonates may develop small airway collapse during normal tidal breathing.

These differences explain the marked changes in FRC in infants after the onset of general anesthesia that is normally not observed in older children and adults. After the administration of sedatives or anesthetics, older children and adults tend to maintain FRC. However, sedated or anesthetized infants will rapidly develop hypoxemia because their tonic muscular contraction that maintains FRC is lost. This loss of FRC can be remedied by application of continuous positive airway pressure (CPAP) or institution of positive-pressure breathing.

The unique anatomic insertion of the infant diaphragm affects respiratory function. At the initiation of inhalation, the newborn diaphragm is relatively flat. Its anterior insertion onto the internal surface of the rib cage confers a mechanical disadvantage during inspiration compared with the high-domed structure of the adult diaphragm. The muscular composition of the newborn's diaphragm is also unique. In contrast to the adult diaphragm, which has a high proportion (50%–60%) of slow-twitch, high-oxidative, fatigue-resistant (type 1) fibers, the newborn diaphragm is made up of only 10% to 30% type 1 fibers. This characteristic predisposes the newborn diaphragm to fatigue, and may contribute to the inherent instability of the chest wall and apnea and respiratory failure in the face of increased ventilatory demands or work of breathing.

On a per-kilogram basis, tidal volume is the same for both neonates and adults and ranges from 7 to 9 mL/kg. Because oxygen consumption is relatively high in neonates and small infants (7–9 mL/kg versus 3 mL/kg for the adult), minute ventilation must be increased to deliver a sufficient amount of oxygen into the lungs (nearly three times that of the adult). As a consequence, small children have a relatively increased ratio of minute volume to FRC. This results in more rapid oxyhemoglobin desaturation during ventilatory depression or apnea.

The generalities are mentioned for discussion purposes only. Research studies demonstrate that respiratory function indices in children are primarily influenced by age, height, gender, stage of puberty, ethnicity, and coexisting disease. Therefore, it would be impossible to predict with any accuracy a given child's tidal volume, FRC, or any other ventilatory function without sophisticated testing.

Hematologic Physiology

At birth, the hemoglobin concentration is approximately 19 g/dL, of which 70% is fetal hemoglobin (Hgb F). This relatively high hemoglobin concentration is needed to offset the leftward shift of the oxyhemoglobin dissociation curve, which causes oxygen to be held tightly by Hgb F. During the first year of life Hgb F is progressively replaced by adult hemoglobin (Hgb A). Production of erythropoietin is absent until hemoglobin levels drop to the physiologic nadir of about 9 to 11 g/dL, between approximately 6 to 9 weeks of age. This is referred to as *physiologic anemia of infancy*. Although this relative anemia may decrease oxygen delivery to the peripheral tissues, it is offset by the increased production of Hgb A and increase in red-cell 2,3-diphosphoglycerate, both of which shift the oxyhemoglobin dissociation curve to the right, which facilitates unloading of oxygen to the peripheral tissues.

TABLE 2.1 Effect of Age on Coagulation Tests[a]

Test	25–31 Weeks Gestation	30–36 Weeks Gestation	Full-Term Newborn	1–10 Years	11–18 Years
Prothrombin time (s)	15.4 (l5–17)	13 (11–16)	15 (14–16)	12 (11.4–13.7)	12.6 (11.4–13.8)
Partial thromboplastin time (s)	108 (80–168)	54 (28–79)	41 (32–47)	37 (31–44)	36 (30–43)
Bleeding time (s)	207 ± 105	157 ± 68	107 ± 38	420 (180–780)	300 (180–480)

[a]Values are mean, approximate normal range in parentheses, and standard deviations for bleeding times for neonatal ages

Coagulation factors are relatively low at birth and normalize within the first year of life (Table 2.1).

Cardiovascular Physiology

Substantial cellular and structural changes occur in the heart in the first several months of life. Neonatal cardiac muscle cells contain all the normal structural elements of the adult heart but are qualitatively and quantitatively different. The pattern of myofilaments is described as chaotic, compared with the long parallel rows of the mature heart. More specifically, the elements of the myocyte that are responsible for contraction are less able to function properly when challenged with a resistive load. Thus, force development is impaired compared with the adult heart, and cardiac output is relatively less in response to changes in preload and afterload. This makes intuitive sense when one considers that during fetal life the left side of the heart had little responsibility against a low-pressure systemic circuit, but in the postnatal period must adapt to a higher stroke volume and increased wall tension.

The postnatal left ventricle develops into a thick organ capable of contracting against higher systemic pressures by increasing the size and number of myocytes. In addition, the shape of the myocyte changes from spheroidal to one with more tapered edges, to increase efficiency of contraction. Factors that increase systemic vascular resistance (e.g., acidosis, cold, pain) in the newborn may lead to a decrease in cardiac output. Therefore, it is possible that intraoperative cardiovascular stability can be enhanced in the newborn by preventing hypothermia and adequately blunting the stress response[1] by titration of opioids. Indeed, a well-publicized, yet controversial, study[2] in newborn cardiac anesthesia suggested that an opioid-based anesthetic technique is associated with improved postoperative cardiac function.

One of the most important clinical correlations of these morphologic differences in the neonate is a decrease in compliance of the left ventricle. The newborn, therefore, is more prone to development of congestive heart failure during periods of fluid overload because the left ventricle is less able to stretch in response to this increase in stroke volume. Also, because of this stiffness, distention of either ventricle will result in compression and dysfunction of the contralateral ventricle, thus further decreasing cardiac function. Newborns with respiratory disease who require high inspiratory pressures may develop left ventricular dysfunction with right ventricular overload. Perhaps more importantly, the newborn left ventricle has an impaired ability to shorten normally, and the heart is less able to increase left ventricular stroke volume during periods of hypovolemia or bradycardia. Thus, episodes of hypovolemia or bradycardia can significantly decrease cardiac output in the neonate, and will endanger end organ perfusion.

Because of these differences in neonatal cardiac function it is often taught that increases in heart rate are needed to increase cardiac output. This should be done with caution, however. Cardiac output will fail to increase substantially if heart rate is increased to levels significantly above normal. Volume expansion also remains an effective method to increase blood pressure and cardiac output during, especially periods of hypovolemia.

Sympathetic innervation of the heart and production of catecholamines, which are not fully developed at birth, increase during postnatal maturation. In contrast, the parasympathetic system appears to be fully functional at birth. Thus, neonates and small infants will demonstrate an imbalance whereby seemingly minor stimuli (e.g., suctioning of the pharynx) result in an exaggerated parasympathetic or vagal response that results in bradycardia. For this reason, pediatric anesthesiologists may administer atropine before airway manipulation in small infants. The belief that bradycardia will result from too small a dose of atropine (<0.1 mg) was ultimately proven erroneous.[3]

These structural and physiologic differences in the cardiovascular system explain why neonates and infants under 6 months of age appear to be more sensitive to the depressant effects of volatile anesthetics. Isoflurane, sevoflurane, and desflurane appear to depress myocardial contractility equally.

The normal heart rate of the newborn ranges from 120 to 160 beats per minute (bpm). Lower rates (e.g., 85 bpm) are frequently observed during sleep, and higher rates

(>200 bpm) are common during anxiety or pain. Heart rates tend to decrease with age and parallel decreases in oxygen consumption. Many children have a noticeable variation in heart rate that varies with respiration (i.e., sinus arrhythmia).

Blood pressure increases gradually throughout childhood[4] and has a positive relationship with height. Taller children have higher blood pressure. These reference values have been retrospectively determined[5] for anesthetized children. Blood pressure ranges in premature infants have been defined[6] and will vary depending on the health status of the infant and mother. One of the most important current topics in pediatric anesthesia is defining the safe limits of blood pressure in young infants. As Mary Ellen McCann points out in her important paper[7] on the topic, these limits have not been delineated. However, there is accumulating evidence that low blood pressures may not be as safe as once thought.

In most children, careful auscultation of the heart reveals a soft, vibratory, systolic flow murmur. A heart murmur is considered abnormal when it is louder than II/VI or has a diastolic component. Peripheral pulses in children of all ages should be clearly palpable. Absence of femoral pulses may indicate an aortic arch abnormality. Capillary refill in the distal extremities should be brisk (less than 2 seconds), but may be slightly delayed in the first few hours of life. Distal limb cyanosis (acrocyanosis) is normal in the first few hours of life.

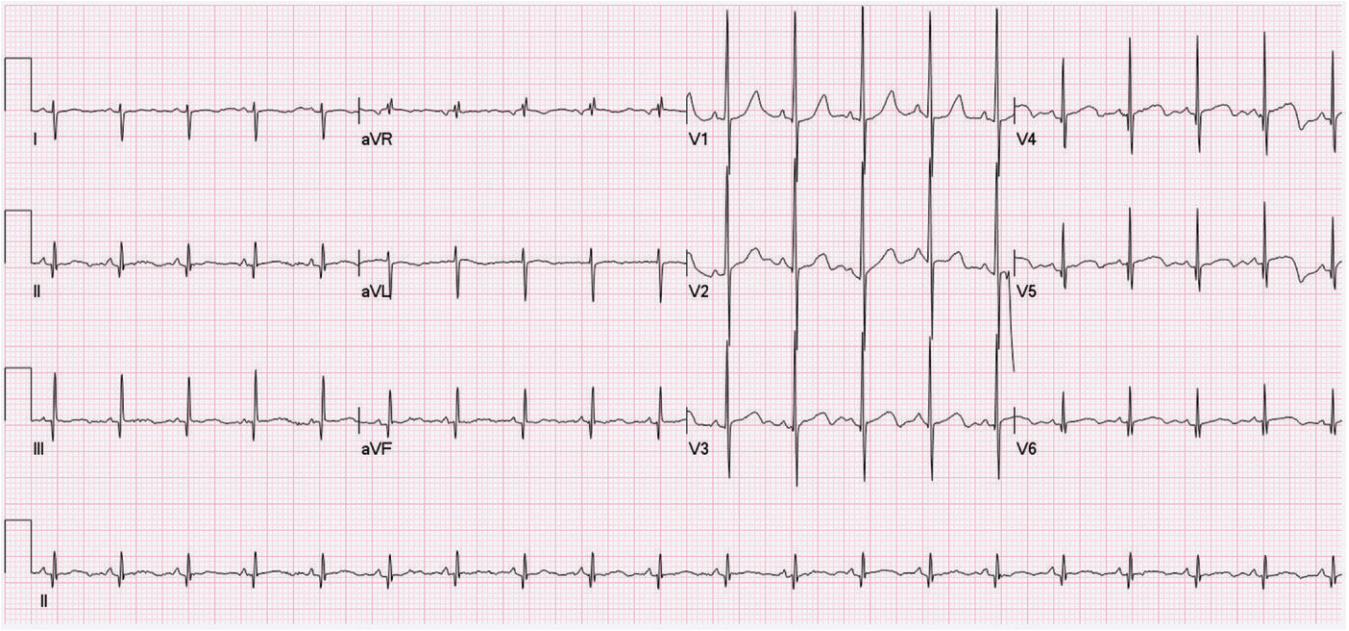
As described in Chapter 1, the fetal heart is characterized by right-sided dominance that gradually abates in the first few months of life as pulmonary pressures decrease toward normal adult values. The normal newborn ECG (Fig. 2.2) demonstrates a preponderance of right-sided forces with a mean QRS axis of +110 degrees (range +30 to +190 degrees), and decreasing R wave size from leads V1 to V6. T waves are normally inverted in lead AVR and the right-sided precordial leads. This gradually shifts to left-sided dominance during early childhood as the left ventricle hypertrophies to its normal size and the ECG becomes more like that of an adult.

The newborn cardiac output (about 350 mL/kg/min) falls over the first 2 months of life to about 150 mL/kg/min and then more gradually to the normal adult cardiac output of about 75 mL/kg/min.

Renal Physiology

By the 36th week of gestation, the formation of nephrons in the kidney is complete. However, the nephrons are small, and the glomerular filtration rate (GFR) is only 25% of adult values at birth. GFR reaches adult levels gradually during the first year of life. Tubular function is also immature; there is a decreased ability to concentrate and dilute the urine in the immediate newborn period. The maximal concentrating ability of the full-term newborn is 400 mOsm/L; the adult value of 1200 mOsm/L is attained by 1 year of age. Therefore, intraoperative evaporative fluid losses may result in development of hypernatremia in the neonate.

In newborn infants, daily fluid intake is gradually increased from 80 mL/kg on the first day of life to 150 mL/kg by the third or fourth day of life. It is adjusted based on additional factors, such as extreme prematurity or use of a radiant warmer, in which evaporative losses from the skin are increased. Neonates who are unable to ingest enteral feeds should receive supplementation of electrolytes (sodium, potassium, and calcium) on the second day of life (Table 2.2).



• **Fig 2.2** Normal newborn ECG. The normal newborn ECG demonstrates a preponderance of right-sided forces, as evidenced by a QRS axis greater than 90 degrees, and decreasing R wave size from right to left in the precordial leads. T waves are normally inverted in lead AVR and the right-sided precordial leads. (ECG courtesy Akash Patel.)

TABLE 2.2 Normal Newborn Daily Electrolyte Requirements

Electrolyte	Average Daily Requirement[a]
Sodium	2–3 mEq/kg
Potassium	1–2 mEq/kg
Calcium[b]	150–200 mg/kg

[a]Adjusted to normal values on a daily basis.
[b]In premature infants under 2,000 g

Central Nervous System Physiology

The skull and CNS undergo substantial postnatal maturation. At birth, the brain is encased within several pieces of the skull that are separated by strong, fibrous, elastic tissues called *cranial sutures*. The anterior fontanel, located at the junction of the frontal and parietal bones, is formed by the intersection of the metopic, coronal, and sagittal sutures. Fusion of these sutures and closure of the anterior fontanel normally closes by 20 months of age. The posterior fontanel, located at the junction of the parietal and occipital bones, is formed by the intersection of the lambdoid and sagittal sutures. The posterior fontanel usually closes by 3 months of age.

The metabolic demand of the brain increases throughout the first year of life and then decreases gradually throughout childhood. The average cerebral metabolic rate of oxygen consumption ($CMRO_2$) of the child's brain (5.2 mL/min of oxygen per 100 g of brain tissue) is greater than the adult's brain (3.5 mL/min/100 g) and greater than that of anesthetized newborns and infants (2.3 mL/min/100 g).

Cerebral blood flow (CBF) is closely coupled to the $CMRO_2$. Whereas in adults the CBF is 50 to 60 mL/min per 100 g of brain tissue, the CBF of term newborns is approximately 40 mL/min/100 g and may be <5 mL/min/100 g in premature infants; in older children the CBF may reach 100 mL/min/100 g.

Autoregulation of CBF is based on systemic blood pressure. While it is thought that autoregulation does occur in newborns its limits are unknown. Extrapolation from animal studies indicates an approximate range of 20 to 80 mm Hg, in contrast to the adult whose autoregulatory limits lie between 60 and 150 mm Hg. Extremely premature infants may have largely pressure-passive CBF that predisposes to brain injury in the face of hypotension or hypertension.

Developmental Pharmacology

The broad subject of pharmacology encompasses the study of pharmacokinetics (the body's influence on the drug) and pharmacodynamics (the drug's influence on the body). Each of these two components is influenced by age and developmental stage. Major differences in pharmacology between adults and children exist because of differences in body composition that influence pharmacokinetics and pharmacodynamics. This section will review the ways in which these factors influence the pharmacology of intravenous and inhaled anesthetics in children.

Pharmacokinetics of Intravenous Anesthetics

The term *pharmacokinetics* describes the physiologic processes that alter a drug's disposition after entering the body. Pharmacokinetic processes determine the amount of drug that arrives at the effect site (the central nervous system for general anesthetic agents) at a given point in time (i.e., the "effect site" concentration) and the speed at which it arrives. The two general pharmacokinetic processes of interest are those that determine the rate and amount of drug that initially reaches the effect site, and those that determine the rate and amount of drug that leave the effect site. These two processes, which are of prime importance to anesthesiologists, are determined by a drug's unique combination of pharmacokinetic parameters: volume of distribution, distribution clearance, protein binding, and elimination clearance (metabolism and excretion). Each of these parameters will be discussed, with an emphasis on the changes that occur during development.

Volume of Distribution

The total (or steady-state) volume of distribution is the calculated amount of plasma into which the drug appears to have distributed at a specified interval after administration. It is not a discrete body compartment but rather is calculated by dividing the dose administered by the plasma concentration. Put another way, the dose of an intravenously administered drug is determined by multiplying the volume of distribution and the desired effect site concentration:

$$Dose\left(\frac{mg}{kg}\right) = Volume\ of\ Distribution\left(\frac{L}{kg}\right) \times Desired\ Effect\ Site\ Concentration\left(\frac{mg}{L}\right)$$

The relative percentage of extracellular and total body water is greatest at birth and declines with advancing age during childhood.[8] Because younger children have a relatively greater amount of extracellular body water and possess adipose stores with a relatively higher ratio of water to lipid than adults, the volume of distribution for water-soluble drugs, such as neuromuscular blockers, will be greater. A larger volume of distribution will be reflected as a larger loading (bolus) dose to achieve the desired plasma concentration and, if clearance is unchanged, a longer half-life.

Protein Binding

Parenterally administered medications are bound primarily to two proteins that are manufactured in the liver: albumin and alpha 1-acid glycoprotein. Albumin binds weak acids (e.g., aspirin), while alpha 1-acid glycoprotein binds weak bases (e.g., local anesthetics). Albumin levels are only slightly

reduced in the newborn period but may have some qualitative immaturity. Alpha 1-acid glycoprotein is not fully produced until sometime in the first year of life. Therefore, drugs such as local anesthetics that are normally bound to alpha 1-acid glycoprotein may have a larger free fraction in the blood of young infants, which predisposes to systemic toxicity.

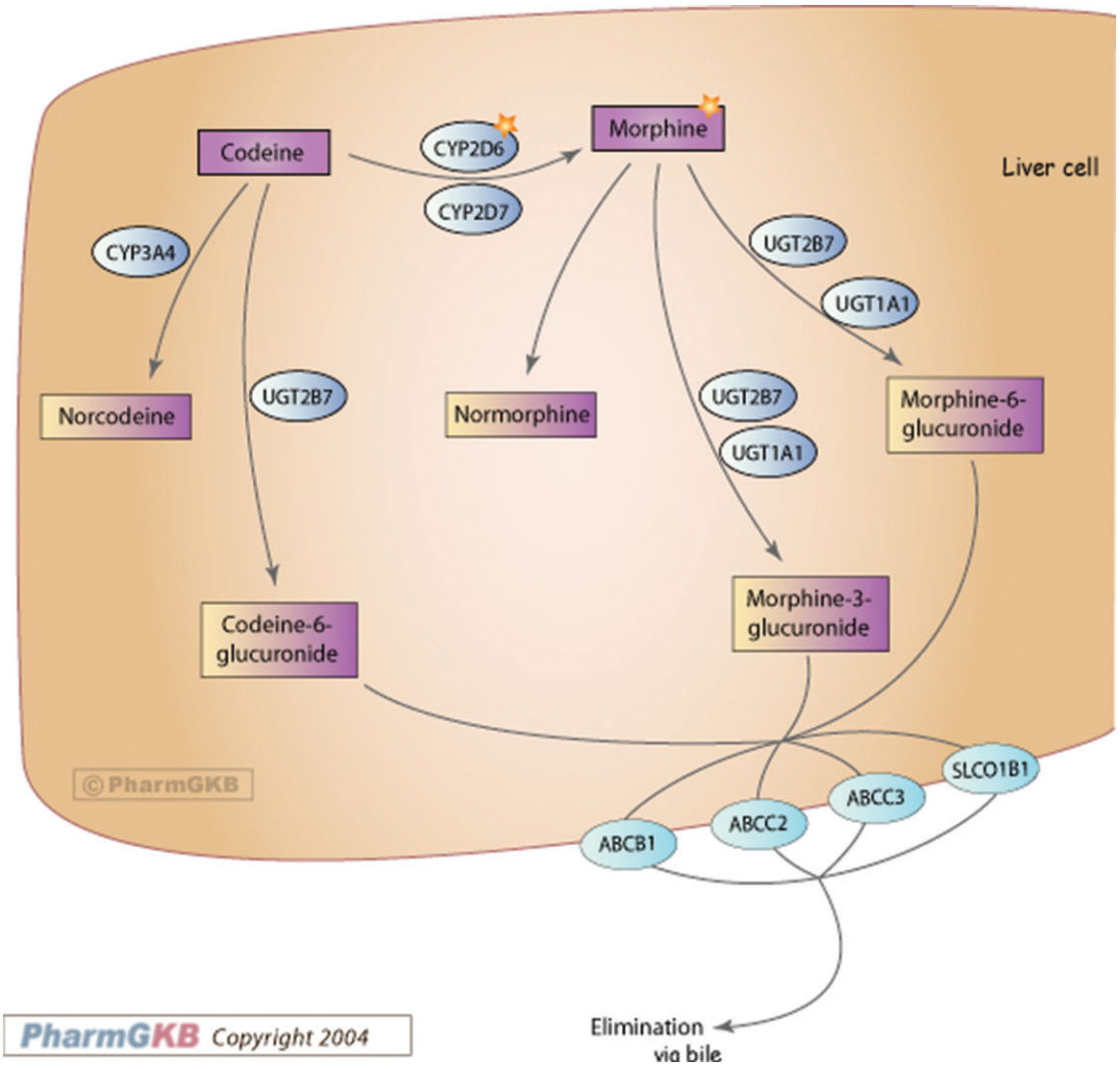
Metabolism

Most intravenously administered anesthetic drugs are lipid soluble and are metabolized in the liver or in the bloodstream. In general, children have more rapid clearance of drugs because of the relatively high proportion of blood traversing the liver. However, in neonates, the phase I (cytochrome-dependent) reactions—oxidation, reduction, and hydrolysis—are not fully developed. Therefore, some anesthetic-related drugs that rely on hepatic metabolism for termination of their action (e.g., vecuronium) may last longer than anticipated. These processes are usually fully functional within the first week after birth. However, the activities of some cytochromes, such as CYP3A4 and CYP3A5 (which metabolize midazolam, for example), continue to increase during the first 3 months of life. It appears that chronologic age, not postconceptional age, is important for development of these metabolic pathways.

Another important example of a cytochrome involved with metabolism of anesthetic drugs is CYP2D6 (Table 2.3 and Fig. 2.3). Levels of this cytochrome

TABLE 2.3 Anesthetic-Related Drugs Metabolized by CYP2D6

- Codeine
- Dexamethasone
- Diphenhydramine
- Lidocaine
- Methadone
- Metoclopramide
- Ondansetron
- Ranitidine



• **Fig 2.3** Codeine metabolism pathway. (Permission from PharmGKB and Stanford University.)

increase greatly and approach adult levels in the first 2 weeks of life. There is a great deal of genetic polymorphism variability of CYP2D6, which renders enzymatic activity from being nearly absent to substantially greater than average. As a result, an individual's metabolic activity can be categorized as *ultrarapid*, *extensive*, *intermediate* (the predominant phenotype), and *poor* (absence of enzyme activity). Poor metabolizers are at risk for drug accumulation and toxicity if the drug cannot be metabolized to its inactive form. Conversely, some drugs, such as codeine and tramadol, require metabolism to a beneficial active form, and thus, these poor metabolizers will not experience a drug effect. Ultrarapid metabolizers, on the other hand, are at risk for opioid toxicity. For these reasons, codeine should not be used to treat postoperative pain (in any aged child) because of the unpredictability of its effect. In fact, the FDA has issued several safety bulletins[9] that addressed this issue. Up to 10% of Caucasians are poor metabolizers, while up to 30% of Middle Easterners and North Africans are thought to be ultrarapid metabolizers.

The phase II reactions consist primarily of conjugation with sulfate, acetate, glucuronic acids, and amino acids. These reactions convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, NH_2, -SH). These reactions are limited at birth but mature within the first few weeks of age, and may differ between classes of drugs.

Excretion

Excretion of intravenous anesthetic drugs is primarily via the kidney. In the first several weeks of life, especially in infants born at less than 34 weeks' gestation, GFR is below normal values, so excretion of drugs may be delayed. After the first several weeks of life, GFR and tubular secretion rise steadily during the first year of life.

Elimination Clearance

Clearance is the volume of plasma that is cleared of drug (by metabolism or excretion) per unit of time. Like the volume of distribution, it is a calculated value that is obtained by dividing the continuous infusion dose of a drug by the resulting plasma concentration:

$$Clearance\,(L/kg/h) = \frac{Dose\,(mg/kg/h)}{Plasma\,Concentration\,(mg/L)}$$

Infants and children tend to have a more rapid clearance of drugs than adults, and for drugs metabolized in the liver, there is an age-dependent increase in plasma clearance up to approximately 10 years of age. The mechanism of this is largely unknown, but it may be related to the fact that the liver receives a proportionately higher fraction of cardiac output in children than in adults.

Pharmacodynamics of Intravenous Anesthetics

Pharmacodynamics refers to the processes that affect the drug's action at a given plasma (or effect site) concentration. Developmental pharmacodynamic differences for most intravenous anesthetic agents are not well studied. However, it appears that neonates may be more sensitive to drugs that act in the central nervous system. This may be due, in part, to an age-dependency for passive diffusion into the brain (i.e., an immature blood-brain barrier) and to relatively greater central nervous system blood flow in neonates and small infants.

Pharmacokinetics of Inhaled Anesthetics

A variety of pharmacokinetic factors can influence the concentration of inhaled anesthetics in the brain and the speed at which this process occurs (i.e., uptake and distribution). The rate of rise of an inhaled anesthetic into the lungs is determined by the delivered concentration of the anesthetic and the minute ventilation of the patient, and is quantitatively described as the alveolar to inspired concentration ratio (F_A/F_I). Compared with adults, children demonstrate a higher minute ventilation per bodyweight and a higher tidal volume to FRC ratio, so the F_A/F_I ratio rises faster during an inhaled induction.

Once in the lungs, uptake of the anesthetic into the bloodstream is determined by the cardiac output, the blood-gas coefficient of the anesthetic agent, and the arterial-to-venous (A-V) concentration difference. All of these factors are influenced by the developmental age of the child.

Cardiac output per bodyweight is relatively higher in children than in adults. A higher cardiac output will tend to slow inhaled induction of anesthesia by removing anesthetic from the alveoli at a more rapid rate.

The blood-gas partition coefficient will determine the speed at which the inhaled anesthetic equilibrates between the alveolar gas and the blood. Although blood-gas partition coefficients have been shown to be lower in small children, it is to an insignificant degree, without clinical importance.

Anesthetic breathed into the alveoli moves into the bloodstream based on the concentration gradient difference between the alveolus and the blood in the pulmonary artery. Therefore, the larger the pulmonary A-V concentration difference, the more rapid the anesthetic will leave the alveoli, slowing the speed of induction. Upon initial uptake of inhaled anesthetic from the alveoli into the bloodstream, the anesthetic will be distributed to the various body tissues. As anesthetic partial pressures in tissues equilibrate with those in the blood, the concentration of the agent that returns to the lungs in the pulmonary artery increases. Consequently, the A-V difference decreases, which reduces the amount of anesthetic agent that is removed from the alveoli. This increases the partial pressure of the anesthetic agent in the alveolus and speeds loss of consciousness. Children demonstrate a faster decrease in the A-V difference because of their

TABLE 2.4 Effect of Age on Body Compartment

	Vessel-Rich		
Age Group	Group	Muscle Group	Fat Group
Newborn	22.0%	38.7%	13.2%
1 year	17.3%	38.7%	25.4%
4 years	16.6%	40.7%	23.4%
8 years	13.2%	44.8%	21.4%
Adult	10.2%	50.0%	22.4%

proportionately larger vessel-rich group that equilibrates anesthetic relatively faster than in adults. As children grow, they increase their content of muscle and fat and take longer to equilibrate inhaled anesthetic (Table 2.4).

The combination of these differences in factors that affect uptake and distribution of inhaled anesthetics results in children demonstrating a more rapid inhaled induction compared with adults.

Pharmacodynamics of Inhaled Anesthetics

The relative potency of inhaled anesthetics, which is quantitatively described as the minimum alveolar concentration (MAC), changes with age.[10] MAC is relatively low for premature infants and gradually increases with age until approximately 6 months of age, after which it tends to decrease with advancing age. The reasons for these changes with age are unknown.

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Suggested Reading

Lambrechts L, Fourie B. How to interpret an electrocardiogram in children. *BJA Educ*. 2020;20(8):266–277. doi:10.1016/j.bjae.2020.03.009.

3

Congenital Heart Disease

ADAM C. ADLER AND RONALD S. LITMAN

The overall incidence of **congenital heart disease (CHD)** is approximately 8 per 1000 live births and is usually divided into two categories: cyanotic (the defect contains a right-to-left shunt) and acyanotic (the defect may contain a left-to-right shunt). The most common cyanotic lesions, in order of decreasing frequency, are **pulmonary stenosis (PS)**, **transposition of the great arteries (TGA)**, **tetralogy of Fallot** (ToF), tricuspid atresia (TA), and pulmonary atresia with intact ventricular septum (PA/IVS). The most common acyanotic lesions, in order of descending frequency, are **ventricular septal defect (VSD)**, **atrial septal defect (ASD)**, aortic stenosis (AS), **coarctation of the aorta (CoA)**, persistent ductus arteriosus (PDA), and complete common atrioventricular canal (CCAVC).

Pathophysiology of Congenital Heart Disease

Anesthesia providers caring for children with CHD must fully understand the anatomic components of the lesion and how the blood flows through the heart and lungs. Because of the complexity of the lesions and subsequent repairs, this can often be confusing. Therefore, a structured approach should be used, with a focus on determining the relative ratios of pulmonary and systemic blood flow. These ratios may ultimately determine the important aspects of anesthetic management. This structured approach involves the following steps:

1. Determine whether blood flow is obstructed in any part of the heart. Right-sided obstructions decrease blood flow to the lungs and result in low PaO_2. Left-sided obstructions decrease blood flow to the body, resulting in decreased tissue perfusion, metabolic acidosis, and shock.
2. Determine whether blood is being shunted from one side of the heart to the other. If blood is shunted from the right side to the left side (e.g., ToF), it does not go through the lungs and results in cyanosis. Left-to-right shunting (e.g., VSD) will result in volume and pressure overload on either or both ventricles and may lead to CHF. In its advanced form, overcirculation of the pulmonary bed leads to pulmonary hypertension and, if untreated, irreversible pulmonary vascular obstructive disease. This results in a reversal of the shunt (to right-to-left) and causes hypoxemia and cyanosis (sometimes known as *Eisenmenger syndrome*). On a basic level, it may seem that the direction of shunting is determined by the location of the defect and obstruction. However, in many cases the resistance in the pulmonary and systemic circuits will determine the direction of shunt. Specialists in CHD like to refer to the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR), also expressed as pulmonary blood flow (Qp) and systemic blood flow (Qs), respectively. This ratio will determine whether the patient has a right-to-left shunt (Qp:Qs <1), a left-to-right shunt (Qp:Qs >1), or both at different times during the cardiac cycle. Other factors, such as ventricular failure or dilation and severe valvulopathy, may also contribute to shunting.
3. Determine whether there is a volume load or a pressure load on the heart. When a ventricle is overburdened by excessive volume overload (e.g., large VSD) or obstruction to forward flow (e.g., right ventricular outflow tract obstruction), the ventricle can begin to fail. In general, the right ventricle responds with dilatation, and the left ventricle with concentric hypertrophy. In either case, when the load exceeds the ventricular capacity, CHF develops. Left-sided CHF often results in pulmonary manifestations and/or systemic hypoperfusion while right-sided CHF can lead to hypoperfusion, hepatomegaly, liver dysfunction, and peripheral edema.

Once these three key points are determined, the anesthesia provider can begin to formulate a plan to safely anesthetize the child with CHD with respect to choice of anesthetic drugs, ventilation strategy and plan for responding to intraoperative cyanosis or hypotension. In the next section, we will take a closer look at the anatomy and physiology of

some of the more common causes of CHD, starting with the acyanotic defects.

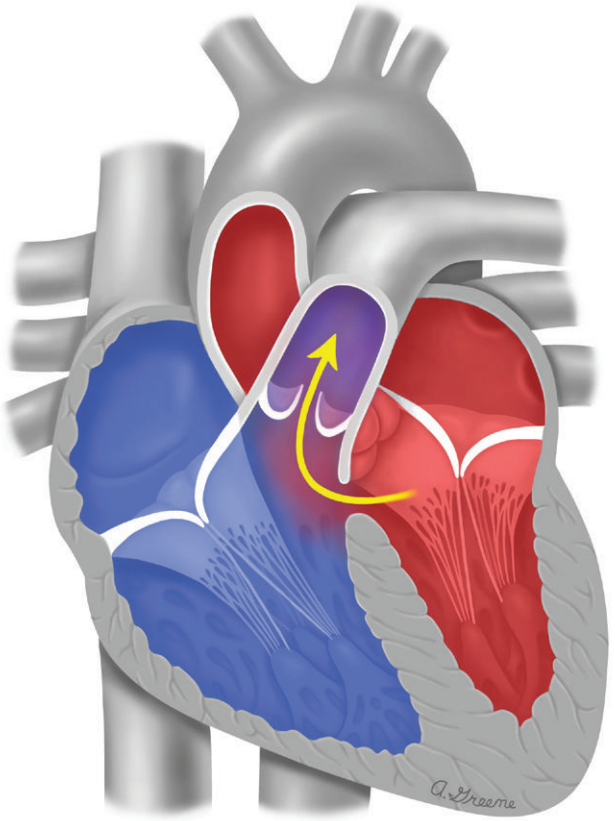
Acyanotic CHD

Ventricular Septal Defect

The most common congenital heart defect (approximately 25% of all congenital cardiac lesions) is the ventricular septal defect (VSD). There are five types of VSD, based on the anatomic location of the defect:

- **Muscular:** occurs in the posterior, apical, or anterior muscular portion of the septum and can be single or multiple.
- **Inlet:** occurs in the part of the septum underneath the septal leaflet of the tricuspid valve.
- **Conoseptal:** occurs in the outflow tract of the right ventricle beneath the pulmonary valve.
- **Conoventricular:** occurs in the membranous portion of the septum.
- **Malalignment:** results from a malalignment of the infundibular part of the septum.

A VSD may be isolated or occur in conjunction with other lesions (Fig. 3.1). The type of VSD does not usually influence anesthetic management; however, when it is excessively large or when associated with other anatomic defects, hemodynamic changes may occur during anesthesia.



• **Fig 3.1. Ventricular septal defect.** (Reproduced with permission from: Fulton DR. Isolated ventricular septal defects in infants and children: anatomy, clinical features, and diagnosis. In: Post TW, ed. UpToDate (website). Accessed on 20.9.22. Available from: www.uptodate.com.)

The clinical features of a VSD are determined by its size and direction of blood flow. If the VSD is relatively small, there are usually no clinical symptoms. A large VSD allows unrestricted blood flow, the direction depending on the PVR to SVR ratio. In almost all children with a VSD, SVR is higher than PVR, and blood flows from left to right through the VSD. If untreated, over time this will result in CHF as the right ventricle becomes overloaded (from the normal venous return plus the extra volume from the left ventricle returning through the VSD). The excessive pulmonary blood flow eventually leads to pulmonary hypertension and reversal of the shunt (right-to-left flow leading to cyanosis).

Treatment of CHF may include digoxin, diuretics, and an angiotensin-converting enzyme (ACE) inhibitor while waiting for natural or surgical closure. Small muscular and conoventricular VSDs close naturally (40% by age 3 years, 75% by age 10 years); however, large VSDs should be closed surgically before pulmonary vascular changes become irreversible. Children with a previous VSD repair may occasionally demonstrate myocardial dysfunction, arrhythmias, or right bundle-branch block.

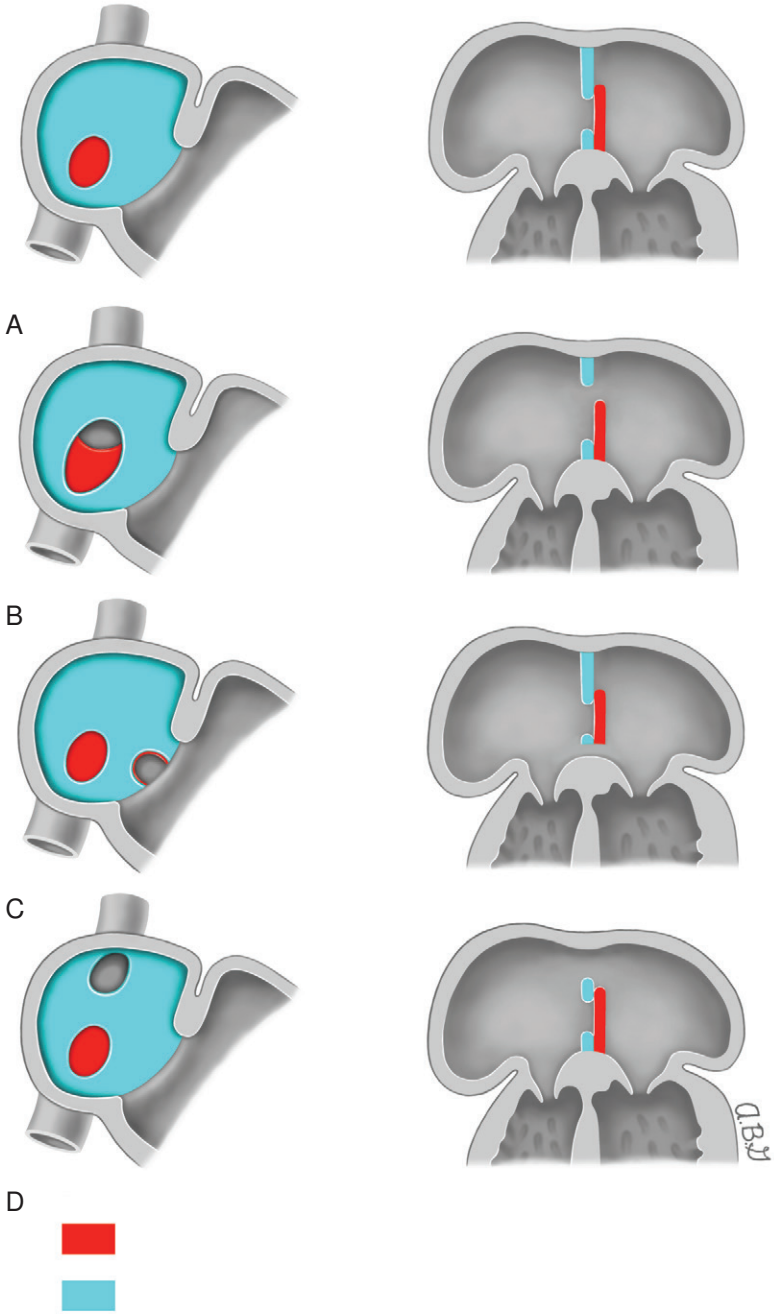
Atrial Septal Defect

Atrial septal defect (ASD) accounts for about 7.5% of CHD. There are multiple types based on the anatomic location of the defect (Fig. 3.2).

- **Ostium secundum:** occurs in the midportion of the atrial septum and is the most common form of ASD.
- **Ostium primum:** occurs low in the atrial septum.
- **Sinus venosus:** occurs at the junction of the right atrium and the SVC or IVC.
- **Coronary sinus:** refers to a hole in the wall of the coronary sinus as it traverses the left atrium.
- **Patent foramen ovale (PFO):** occurs when there is inadequate fusion of the septum secundum and the septum primum.

Nearly all small secundum type ASDs close spontaneously during the first year of life. However, large secundum ASDs, or those with significant shunting, will require surgical repair or placement of a closure device via cardiac catheterization.

Ostium primum, sinus venosus, and coronary sinus ASDs do not close spontaneously and must be closed surgically. PFOs occur in about 20% to 30% of the general population. Children are usually asymptomatic after ASD repair. Although there are no unique anesthetic considerations for noncardiac surgery, careful attention must be paid to de-bubbling the intravenous lines. Air bubbles that enter into the venous system may cross over to the arterial system and cause a clinically significant air embolus in the cardiac or cerebral arteries. The specific type of ASD does not influence anesthetic management unless it causes physiologic abnormalities.



• **Fig 3.2.** Arterial septal defects. (Panel A) The normal atrial septum and various types of atrial septal defects (ASD) are shown. (Panel B) Secundum ASD is formed by the poor growth of the septum secundum or excessive absorption of the septum primum. (Panel C) Primum ASD is formed by the failure of the septum primum to fuse with the endocardial cushions. The fossa ovalis is normal. The frontal view of the primum ASD shows the caudal location of the ASD just above the endocardial cushion. (Panel D) Sinus venosus ASD is caused by the malposition of the insertion of the superior or inferior vena cava and is outside the area of the fossa ovalis. (Reproduced with permission from: Wick GW, Bezold LI. Isolated atrial septal defects (ASDs) in children: classification, clinical features, and diagnosis. In: Post TW, ed. *UpToDate* (website). Accessed on 20.9.22. Available from: www.uptodate.com.)

Complete Common Atrioventricular Canal

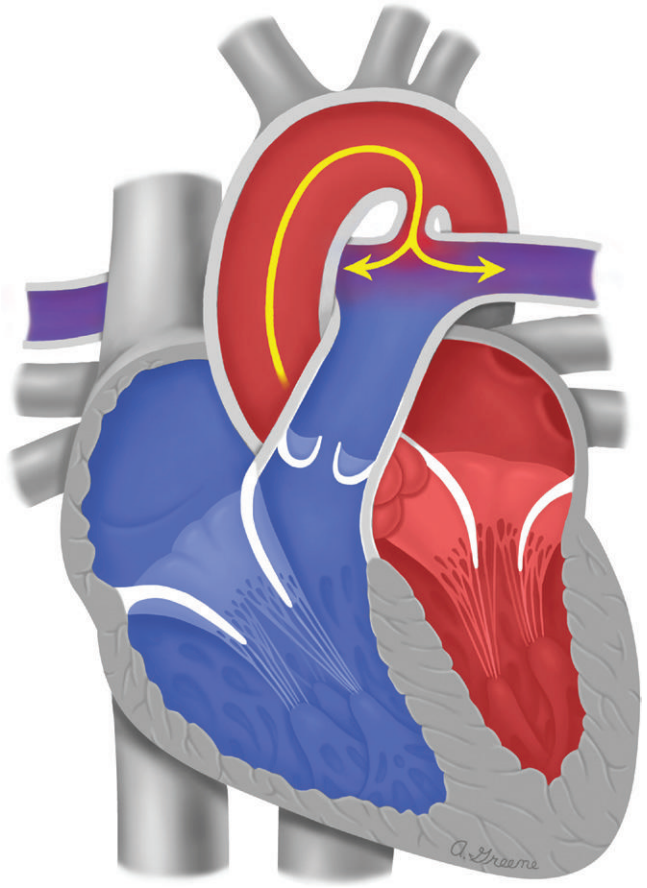
Complete common atrioventricular canal (CCAVC, also referred to as an *endocardial cushion defect*) consists of an ostium primum ASD and a nonrestrictive inlet VSD, and often occurs in children with trisomy 21. There is usually a left-to-right shunt at the atrial and ventricular levels which can result in CHF during infancy. Pulmonary hypertension may develop from the increase in pulmonary blood flow.

Surgical repair of CCAVC is usually performed in the first year of life. Complete heart block occurs in 5% of patients undergoing repair, and residual mitral insufficiency may be seen.

Patent Ductus Arteriosus

Before birth, blood bypasses the lungs and travels from the main pulmonary artery to the descending aorta through the ductus arteriosus (Fig. 3.3). Normally, there is *physiologic* ductus closure in the first days of life (because of pressure differences in the aorta and pulmonary artery) and *anatomic* closure in the first months of life. In certain conditions such as prematurity, the ductus remains patent indefinitely and serves as a source of left-to-right shunt and right-sided pulmonary overcirculation. **Patent ductus arteriosus (PDA)** represents approximately 7.5% of congenital heart disease.

A variety of factors tend to contribute to patency of the ductus arteriosus, such as hypoxemia, respiratory or metabolic acidosis, and persistent pulmonary hypertension of the newborn. The direction of shunted blood through a large PDA depends on the ratio of PVR to SVR. In a nonrestrictive PDA, a left-to-right shunt occurs if SVR is greater than PVR. Newborns with a large PDA and left-to-right shunt may show signs of pulmonary overcirculation and CHF, which include a widened pulse pressure, a continuous murmur, and an inability to wean ventilatory parameters. Treatment usually consists of diuretics until the PDA can be closed either medically, with administration of indomethacin, or surgically with an open or video-assisted catherization device closure (coil embolization).



• **Fig 3.3.** Patent ductus arteriosus. (Reproduced with permission from: Doyle T, Kavanaugh-McHugh A. Clinical manifestations and diagnosis of patent ductus arteriosus in term infants, children, and adults. In: Post PW. *UpToDate* (website). Available from: www.uptodate.com.)

It is crucial to identify ductal-dependent lesions in the newborn, in which patency of the ductus arteriosus is not only favorable but required for survival. These include cyanotic lesions such as pulmonary atresia/stenosis, tricuspid atresia/stenosis, and transposition of the great arteries, and some acyanotic lesions, such as coarctation of the aorta, hypoplastic left heart syndrome, critical aortic stenosis, and interrupted aortic arch. As soon as a ductal-dependent lesion is discovered, a prostaglandin E1 (PGE1; alprostadil) infusion is started at 0.05 to 0.1 mcg/kg/min. Infants should be monitored for apnea during administration of PGE1, and are maintained at relatively low concentrations of oxygen to encourage ductal patency.

Aortic Stenosis

Aortic stenosis (AS) represents up to 5% of CHD. It ranges in severity from mild to severe, or complete aortic atresia as seen in hypoplastic left heart syndrome (see below). The neonate with critical AS relies on their PDA for systemic blood flow; if the PDA closes, circulatory shock will occur. Most cases of mild AS are detected later in childhood by the presence of a murmur.

The clinical manifestations of AS will depend on the degree of stenosis and the ventricular function. Significant stenosis produces a large pressure gradient between the left ventricle and the aorta resulting in left ventricular hypertrophy with subsequent decreased ventricular compliance and function.

Hemodynamically significant AS requires surgical intervention, which is accomplished by balloon valvuloplasty or open surgical valvotomy. In some cases, treatment of AS causes aortic regurgitation, which may eventually require aortic valve replacement. In some children, a Ross procedure (pulmonary autograft) is performed, in which the child's own pulmonary valve is moved into the aortic position, and a right ventricle-to-pulmonary artery homograft conduit is placed.

Coarctation of the Aorta

Coarctation of the aorta (CoA) represents about 8% of all congenital heart defects, of which approximately 80% also have a bicuspid aortic valve. It usually occurs distal to the origin of the left subclavian artery at the insertion site of the ductus arteriosus. The coarctation narrows the aorta, thus increasing left ventricular afterload. CHF develops in about 10% of cases in infancy. There is a 15% to 20% risk for having CoA in girls with Turner syndrome (45, XO).

Neonates with severe CoA need their PDA to provide blood to the systemic circulation. If the PDA closes, the infant goes into circulatory shock. Therefore, PGE1 is administered to keep the ductus open until the CoA is repaired. More commonly, CoA presents during childhood.

Typically, it is diagnosed during investigation of a new heart murmur, accompanied by hypertension of the upper extremities and decreased or absent femoral pulses. Left ventricular hypertrophy and CHF can result from chronic pressure overload.

The CoA can be treated by balloon dilation angioplasty, stent placement, surgical end-to-end anastomosis, subclavian flap repair, or graft placement. In many patients hypertension persists throughout childhood; the duration of postoperative hypertension correlates with the duration of hypertension before the repair.

Cyanotic Congenital Heart Diseasae

D-Transposition of the Great Arteries

D-transposition of the great arteries (TGA) accounts for about 5% of CHD and is the most common form of cyanotic CHD in the neonatal period. In TGA, the great vessels are transposed, which means that the aorta arises from the right ventricle, and the pulmonary artery rises from the left ventricle. Thus, circulation exists as two separate parallel circuits unless a communication (PDA, VSD, or PFO) can mix the blood to maintain survival. Infants with TGA will appear cyanotic shortly after birth when the PDA functionally closes. As soon as the diagnosis is made by echocardiogram (or even before), PGE1 is administered to maintain ductal patency, and the infant is considered for emergent balloon atrial septostomy in the cardiac catheterization lab to allow more complete mixing at the atrial level through an unrestricted communication.

Treatment for TGA requires the arterial switch operation[1] usually within the first 2 weeks of life. Survival exceeds 95%. Left ventricular function usually remains good throughout childhood, although supravalvular pulmonary stenosis may remain and require intervention. Occasionally, children will demonstrate atrial and ventricular tachyarrhythmias.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is the second most common type of cyanotic CHD. It presents in the first week of life, and is the most common cause of death from CHD in the first month of life. HLHS consists of hypoplasia of the left ventricle, aortic valve stenosis or atresia, mitral valve stenosis or atresia, and hypoplasia of the ascending aorta with a discrete CoA. The result is the lack of blood flow through the left heart, causing an obligatory left-to-right shunt at the atrial level and a right-to-left shunt through a PDA. Systemic flow becomes completely dependent on the PDA, and coronary perfusion is retrograde in the presence of aortic atresia or critical aortic stenosis. The diagnosis of HLHS is often made *in utero* or in the first few days of life when the PDA closes and the infant presents in heart failure and shock. Clinical signs include tachycardia, tachypnea, pulmonary rales (from pulmonary edema), hepatomegaly, and poor peripheral pulses with diminished distal capillary refill. PGE1 is started immediately upon diagnosis to maintain ductal patency, and the infant is prepared for urgent surgery.

In most centers, treatment consists of a three-stage surgical correction performed over the first several years of life. In the first week of life, a Norwood procedure is performed to create a "neo-aorta" to establish unobstructed systemic blood flow. This allows the majority of neonates with HLHS to survive infancy. The single right ventricle provides systemic blood flow, and pulmonary blood flow is provided by placement of a modified Blalock–Taussig (subclavian-to-pulmonary artery) shunt (see below) or a right ventricle-to-PA conduit (Sano shunt). An atrial septectomy (or permanent ASD creation) is performed to create an unobstructed atrial communication to allow oxygenated blood flow to return from the lungs and reach the systemic circulation. After this initial stage the patient's oxygen saturation is usually 60% to 75%.

The second stage is usually performed between 4 and 6 months of age. The procedure is known as a hemi-Fontan (also called *bidirectional Glenn* or *Norwood 2*). The SVC is anastomosed to the right PA, so that blood returning from the head bypasses the right ventricle and flows passively into the pulmonary circulation. This procedure is delayed until the patient's PVR, which continues to drop after birth, decreases to the point at which the lungs are able to accept the additional blood flow. The second stage also decreases the effective blood flow load on the single ventricle. At this age, the patient does not require their BT shunt, as the newly created SVC-to-PA anastomosis serves as the source of pulmonary blood flow. After this stage, the patient's oxygen saturation is usually 70% to 85%.

The third stage, performed at approximately 2 to 3 years of age, is the completion Fontan, in which the IVC is joined directly to the pulmonary artery. After this procedure, all venous blood returning to the heart bypasses the single ventricle heart and flows passively into the lungs, while the single right ventricle serves to pump oxygenated blood returning from the lungs to the body. After this stage, the patient's oxygen saturation now approaches normal values for the first time. Patients with a fenestrated Fontan (a small hole or connection between the IVC-PA connection and the atrium) may serve as a source of right-to-left shunt reducing the patient's normal saturation. Shunting across the fenestration occurs during times of elevated pulmonary pressure.

The circulation that remains is referred to as *Fontan physiology*. Blood flow to the lungs becomes dependent on the transpulmonary gradient, which is the pressure difference between the Fontan circuit (systemic veins and pulmonary arteries) and the pulmonary venous atrium. Thus, any condition that increases PVR will decrease blood flow through the lungs and cause hypoxemia (Table 3.1).

A number of perioperative factors can decrease pulmonary blood flow. After a Fontan procedure, patients may develop atrial arrhythmias or complete heart block. These arrhythmias are poorly tolerated because of the relatively large contribution of atrial contraction to ventricular filling.

TABLE 3.1 Determinants Of Pulmonary Blood Flow

Factors that Increase Pulmonary Blood Flow	Factors that Decrease Pulmonary Blood Flow
• Decreased PVR • Hyperoxia • Hypocarbia • Alkalosis • Hypertension or increased SVR (e.g., inotropic therapy) in patients with single-ventricle physiology • Low mean airway pressure	• Increased PVR • Hypoxia • Hypercarbia • Acidosis • Hypotension or lowering of SVR (e.g., inhaled anesthetics) in patients with single-ventricle • physiology • Positive end-expiratory pressure (PEEP)

Adult patients with Fontan physiology may progressively develop myocardial failure, which sometimes manifests as ventricular arrhythmias.

Inhaled anesthetics decrease SVR by dilating arteriolar and venous beds, resulting in a decrease in venous return. This may critically limit pulmonary blood flow by decreasing the transpulmonary gradient. In a patient with Fontan physiology, positive-pressure ventilation can also decrease pulmonary blood flow. Positive end-expiratory pressure (PEEP) and elevated mean airway pressures can impede venous return and decrease pulmonary blood flow. These patients may become hypotensive during induction of anesthesia, or with prolonged NPO duration or gastrointestinal (GI) illnesses. Patients with Fontan circulation require judicious fluid monitoring and the shortest possible NPO times. Spontaneous ventilation is preferred in these patients as negative intrathoracic pressure increases the gradient between extrathoracic and intrathoracic pressures and results in increased flow through the pulmonary circulation. Preferred anesthetic techniques in the Fontan patient include use of a face mask or supraglottic airway with spontaneous ventilation, or a regional technique with IV sedation. However, atelectasis is likely in longer cases, in which controlled ventilation may be the most prudent option, with the goal of immediate tracheal extubation at the completion of the procedure.

Pulmonary Stenosis

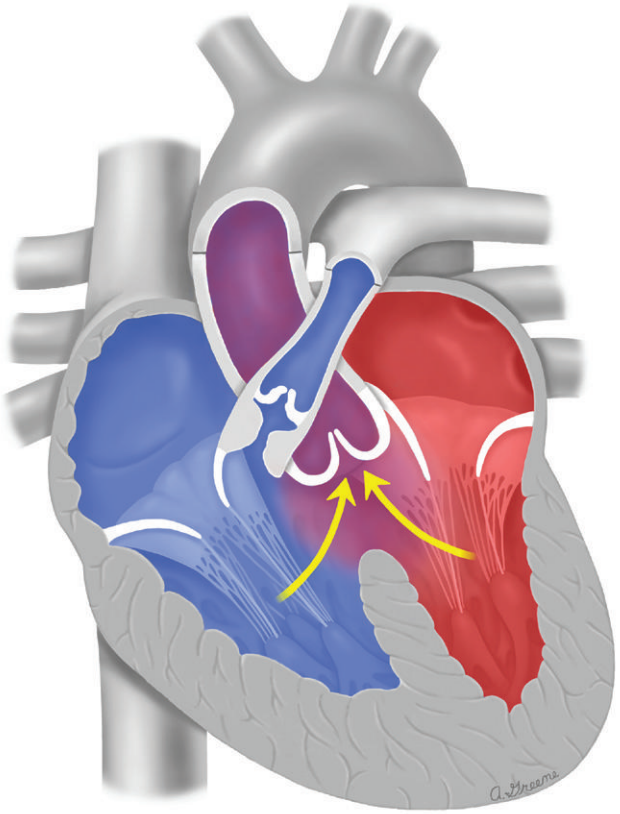
Pulmonary Stenosis (PS) accounts for approximately 8% of all CHD and usually occurs at the level of the valve, although subvalvular and supravalvular stenoses may occur. It can also occur as a component of other heart defects, especially tetralogy of Fallot. The clinical manifestations of PS depend on the degree of valve restriction. Right ventricular hypertrophy occurs as the ventricle attempts to maintain cardiac output. Symptoms of severe PS include CHF and cyanosis.

Moderate and severe PS (gradient ≥50 mm Hg) are treated with balloon valvuloplasty. Open surgical repair may be necessary in some cases. Once dilated or repaired, children with isolated PS are relatively healthy and usually present no further anesthetic considerations.

PS should not be confused with peripheral pulmonic stenosis, which is a benign condition of the newborn that produces a murmur as a result of the acute angle of bifurcation of the main pulmonary artery.

Tetralogy of Fallot

After the immediate newborn period, tetra of Fallot (ToF) (Fig. 3.4) is the leading cause of cyanotic CHD. ToF encompasses four defects: typically, infundibular hypoplasia (the area between the aortic and pulmonary valves) results in a shift of tissue to the right compressing the right ventricular outflow tract to varying degrees. The right ventricular outflow tract obstruction results in compensatory right ventricular hypertrophy. This movement also includes a portion of the ventricular septum resulting in an anterior malalignment VSD together with the aorta which overrides the VSD. Cyanosis results from right-to-left shunting across the VSD and decreased pulmonary blood flow caused by the right ventricular outflow tract obstruction. The degree of right ventricular outflow tract obstruction determines the overall severity of the defect.



• **Fig 3.4.** Tetralogy of Fallot. (Reproduced with permission from: Doyle T, Kavanaugh-McHugh A, Graham, Jr, TP. Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot. In: Post PW. *UpToDate* (website). Available from: www.uptodate.com. Accessed 04/29/2022)

If ToF is not corrected during infancy, the child may experience sudden episodes of cyanosis secondary to infundibular spasm that worsens right ventricular outflow tract obstruction. These are commonly known as *Tet spells*, and they may last minutes to hours. They usually resolve spontaneously but might lead to syncope, progressive hypoxia, or death. Tet spells can occur at any time in the perioperative period and can be treated by diminishing right-to-left shunting by increasing SVR and decreasing PVR. They are treated by a stepwise approach, consisting of placing the child in the knee-chest position, administration of a sedative, such as an opioid or benzodiazepine, administration of a beta-blocker, such as propranolol or esmolol, or administration of phenylephrine.

ToF is usually repaired within the first 6 months of life, depending on the anatomic variation. Pulmonary stenosis and right ventricular outflow tract obstruction are managed initially by balloon angioplasty followed by patch VSD closure. Postoperatively, these infants commonly exhibit some degree of residual pulmonary insufficiency and right bundle-branch block. Ventricular arrhythmias may occur in adolescence when there is pulmonary insufficiency and right ventricular dilatation or dysfunction.

Tricuspid Valve Atresia

Tricuspid valve atresia (TA) leads to hypoplasia or absence of the right ventricle. An associated VSD is found in 90% of TA cases. Blood passes from the right atrium to the left atrium and into the systemic circulation via the aorta or the lungs via the ductus arteriosus. The VSD allows blood to pass from the left ventricle to the right ventricle and into the pulmonary artery, however, the majority of patients with TA also have pulmonary stenosis. Newborns with TA manifest cyanosis, poor feeding, and tachypnea within the first 2 weeks of life. Cyanosis in the neonatal period is correlated with the amount of restriction of pulmonary blood flow. PGE1 is administered to maintain ductal patency and pulmonary flow, and a balloon atrial septostomy is performed if the atrial defect is not adequate. Surgical management involves placing a modified Blalock–Taussig shunt to maintain pulmonary blood flow. Later in infancy, a cavopulmonary anastomosis (hemi-Fontan or bidirectional Glenn) is performed to provide stable pulmonary blood flow. In most centers, a modified Fontan procedure is performed to redirect the inferior vena cava and hepatic vein flow into the pulmonary circulation. Compared with HLHS patients, these children usually benefit from having the left ventricle remain the primary pumping chamber for the systemic circulation.

Anesthetic Management of Children With CHD

Preoperative Assessment

The extent of the preoperative evaluation depends on the underlying diagnosis, degree of hemodynamic stability, and coexisting medical conditions. The anatomic and hemodynamic function of the child's heart should be mapped out, and previous anesthetics reviewed. Children that are currently under the care of a cardiologist should have an updated consult that includes a description of the child's cardiac anatomy.

The best way to determine the child's functional status is to assess limitations of daily activities and exercise. The feeding patterns of infants may provide a clue to cardiac function because of the physical effort involved to coordinate suck and swallow. Cardiac reserve is likely reduced if an infant is unable to finish a feed without tiring, or develops cyanosis, diaphoresis, or respiratory distress during feeding. Smaller children with limited cardiac output and increasing oxygen consumption will demonstrate failure to thrive or decreased normal activity. Older children may become more sedentary. Syncope, palpitations, and chest pain are additional symptoms of cardiac limitation that should be investigated before elective surgery.

Medications administered to children with CHD include diuretics, afterload reduction agents, antipulmonary hypertensives, antiarrhythmics, antiplatelet or anticoagulation drugs, and possibly inotropic or immunosuppressant agents in heart transplant recipients. All scheduled medications should be taken on the day of surgery, except for diuretics, which are usually withheld, depending on the clinical condition of the child. Children taking diuretics should have a preoperative evaluation of electrolytes.

Preoperative laboratory or diagnostic testing will depend on the nature of the child's disease and recent manifestations. A hemoglobin level may be indicated for children with cyanotic CHD who compensate for chronic hypoxemia by developing polycythemia. A hematocrit that approaches 65% will increase blood viscosity and interfere with tissue microcirculation, contribute to tissue hypoxia, increase SVR, and predispose to venous thrombosis and strokes. A normal or low hematocrit may indicate relative anemia, and is usually caused by iron deficiency. Iron-deficient red blood cells are less deformable and increase blood viscosity. Anemia or polycythemia should be evaluated and corrected before elective surgery. This is often done in consultation with the patient's cardiologist and/or hematologist.

Preoperative vital signs, including room air SpO_2, are used as a baseline to determine intraoperative norms. Baseline heart sounds, and the presence of cyanosis or pallor should be noted. The presence of tachypnea or rales on lung auscultation may indicate pneumonia or CHF. An upper respiratory tract infection warrants particularly careful evaluation and possible cancellation, as it may lead to complications in children with CHD, especially when caused by respiratory syncytial virus (RSV).

CHD may be accompanied by tracheobronchial anomalies, such as shortening or stenosis, and may remain unrecognized until endotracheal intubation is required. This is particularly true for children with trisomy 21. A history of prolonged intubation after CHD surgery raises the

possibility of an airway abnormality. Inspiratory stridor is an indication of airway narrowing because of subglottic stenosis or a vascular malformation that causes compression of the lower airway.

Neurologic abnormalities are not uncommon in children with CHD. The presence of a right-to-left shunt with polycythemia may predispose to an embolic stroke. Cardiopulmonary bypass is associated with microemboli that travel to the brain and cause vascular occlusion.

Preoperative dehydration may be hazardous in children with cyanotic CHD and polycythemia. Attention to preoperative oral or IV hydration is especially important for children with ToF, cyanotic patients with polycythemia, and children with Fontan physiology. Dehydration may cause ToF patients to have a hypercyanotic Tet spell. Fontan patients are dependent on venous return for pulmonary blood flow; thus, dehydration may lead to decreased central venous pressure and subsequent decreased pulmonary blood flow and poor cardiac output. These patients may benefit from preoperative admission for overnight hydration. Fasting intervals should be no different for children with CHD than for healthy children and drinking clear liquids 1 to 2 hours before planned induction of general anesthesia should be encouraged.

Premedication with oral midazolam is useful to allay preoperative anxiety, and even hemodynamically unstable children can receive carefully titrated IV midazolam. The advantages of preoperative anxiolysis in children with CHD include easy separation from parents, less crying, decreased oxygen consumption, and decreased levels of intraoperative anesthetics. Some anesthesiologists fear that even minimal respiratory depression caused by sedatives may cause significant oxyhemoglobin desaturation in children with cyanotic CHD whose resting oxyhemoglobin saturations lie on the steep portion of the hemoglobin dissociation curve. However, several investigations that assessed this risk demonstrated that preoperative anxiolysis resulted in less oxyhemoglobin desaturation during induction of anesthesia.

Subacute Bacterial Endocarditis (SBE) Prophylaxis

The American Heart Association published updated guidelines[2] in 2015 on administration of prophylactic antibiotics to prevent infective endocarditis (IE), an infection of the endocardial surface of the heart, in susceptible children. The mechanism of IE involves endothelial damage with platelet and fibrin deposition, which allow for bacterial colonization. "Subacute" refers to the slow and often ambiguous onset and detection of the infection in patients with preexisting heart disease, and is associated, generally, with good outcomes. Perioperative antibiotics are recommended for dental procedures that involve manipulation of gingival tissue or perforation of oral mucosa in the following types of high-risk patients who have cardiac conditions that include the following:

- Prosthetic cardiac valves
- Previous endocarditis
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired CHD repaired with prosthetic material or device, whether placed surgically or by catheter intervention, during the first 6 months after the procedure
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplant recipients with valve regurgitation because of a structurally abnormal valve

Antibiotic prophylaxis for IE is no longer recommended for patients (without an active infection) undergoing GI and genitourinary (GU) procedures, transesophageal echocardiograms, and respiratory tract procedures, unless there is an incision of the mucosa. Respiratory procedures that should be covered include tonsillectomy, adenoidectomy, bronchoscopy, nasotracheal intubation, and any other procedure that involves an incision of the respiratory mucosa. Note that the recommended SBE prophylaxis dose is typically greater than the standard dose for surgical site infection prophylaxis and dose adjustments should be made accordingly (Table 3.2).

Anesthetic Techniques in Children With CHD

By virtue of their propensity to cause hemodynamic compromise in susceptible CHD patients, there is no anesthetic regimen that is inherently safer than any other. All volatile anesthetics can alter PVR, SVR, myocardial contractility, heart rhythm, heart rate, and shunt flow. In healthy patients, isoflurane produces a drop in SVR by vasodilation, which may decrease mean arterial pressure. In children with CHD, isoflurane slightly increases heart rate and tends to maintain cardiac index. In normal children and in those with CHD, sevoflurane decreases SVR and can decrease the LV shortening fraction, yet cardiac index and heart rate are maintained. Sevoflurane can also produce diastolic dysfunction. Nitrous oxide produces minimal myocardial depression, and although it is associated with increased PVR in adults, it produces minimal changes in infants with both normal and increased PVR. Nitrous oxide can, however, increase the size of an air embolus.

In children with right-to-left shunts, inhaled induction may result in an increased shunt fraction and cyanosis secondary to a decrease in SVR. In these children, a slow titration of agent is necessary with frequent measurements of blood pressure. The occurrence of hypoxemia that is not the result of respiratory causes should be attributed to systemic vasodilation and right-to-left shunting and should be treated with a direct vasoconstrictor such as phenylephrine.

Intracardiac shunts can affect the rate of anesthetic induction. In the presence of a right-to-left shunt, dilution of anesthetic agent in the left ventricle by venous blood that bypasses the lung results in a decreased concentration

TABLE 3.2 Regimens for Antimicrobial Prophylaxis for a Dental Procedures

Regimen: Single Dose 30–60 min Before Procedure			
Situation	**Agent**	**Children**	**Adults**
Oral	Amoxicillin	50 mg/kg	2 g
Unable to take oral medication	Ampicillin	50 mg/kg, IM or IV	2 g, IM or IV
Allergic to penicillins or oral ampicillin	Cephalexin[b,c]	50 mg/kg	2 g
		OR	
	Clindamycin	20 mg/kg	600 mg
		OR	
	Azithromycin or clarithromycin	15 mg/kg	500 mg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[e]	50 mg/kg, IM or IV (cefazolin); 50 mg/kg, IM or IV (ceftriaxone)	1 g, IM or IV
		OR	
	Clindamycin	20 mg/kg, IM or IV	600 mg, IM or IV

IM, intramuscular; *IV*, intravenous.
[a]Pediatric dosage should not exceed recommended adult dosage.
[b]Or other first- or second-generation oral cephalosporin in equivalent pediatric or adult dosage.
[c]Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
(From: Baltimore RS, Gewitz M, Baddour LM, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young and the Council on Cardiovascular and Stroke Nursing. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. *Circulation*. 2015;132(15):1487–1515.)

of agent reaching the brain. This will, theoretically, slow the rate of induction of anesthesia. Conversely, left-to-right shunts may speed induction of anesthesia by rapidly decreasing the arterial-to-venous difference of agent in the lungs. In clinical practice, these effects are hardly noticeable.

Small amounts of air trapped in IV tubing that enters the circulation can cause complications in children with CHD. Therefore, IV lines must be de-aired before connection. With a right-to-left shunt, an injected air bubble can cross into the systemic circulation and cause a stroke if it passes from the aorta to the brain via a carotid or vertebral artery or result in other end organ damage. With a left-to-right shunt, air bubbles pass into the lungs and are absorbed.

High oxygen concentrations decrease PVR and increase SVR; hypoxemia increases PVR and decreases SVR. These changes may significantly alter pulmonary blood flow by changing the PVR to SVR ratio in the presence of a large, unrestrictive intracardiac shunt.

Intravenous induction of general anesthesia with propofol can be accomplished by titrating the drug judiciously, depending on the patient's tolerance for changes in heart rate and blood pressure. In theory, a left-to-right shunt will slow IV induction and a right-to-left shunt will speed the time of induction by shunting more anesthetic agent to the brain without passing first through the lungs. But as with inhaled induction, these effects are difficult to appreciate clinically.

Ketamine, etomidate, and dexmedetomidine may provide greater hemodynamic stability in children with CHD. The sympathomimetic effects of ketamine tend to maintain heart rate, contractility, and SVR. There are theoretical concerns with ketamine's ability to cause an increase in PVR, especially in patients with Fontan physiology. However, this has not been substantiated in clinical studies performed in children with CHD. For the most part, opioids and benzodiazepines are safe in children with CHD as long as clinically significant bradycardia is avoided.

Regional anesthesia should be encouraged in children with CHD but with several caveats:

1. The child with longstanding CoA and dilated tortuous intercostal arteries is at risk for arterial puncture or excessive absorption of local anesthetic during intercostal blockade.
2. Because the lungs may absorb up to 80% of the local anesthetic on first passage, the risk for local anesthetic toxicity is theoretically increased in a patient with a right-to-left shunt because the brain will be exposed to a higher concentration than usual.
3. Vasodilatation resulting from central axis blockade may be hazardous in patients with left-sided obstructive lesions. Vasodilatation may also cause a decrease in oxyhemoglobin saturation in children with a right-to-left shunt. On the other hand, peripheral vasodilatation in patients with polycythemia may have the benefit of improved microcirculatory flow and decreased venous thrombosis.
4. Children with chronic cyanosis are at risk for coagulation abnormalities and should be adequately evaluated before initiation of regional anesthesia.

Monitoring Children with CHD

Pulse oximetry reliably predicts oxyhemoglobin saturation in the range that is normally encountered in children with cyanotic CHD (SpO_2 70%–90%). However, it may have limited accuracy at oxyhemoglobin saturations below 70%, and should be verified by blood gas analysis when in question.

Intraoperative $P_{ET}CO_2$ monitoring can be unreliable in children with CHD. $P_{ET}CO_2$ will tend to underestimate $PaCO_2$ because abnormal pulmonary ventilation/perfusion ratios result in increased dead space and/or shunt, which alter the arterial-to- $P_{ET}CO_2$ difference.

Blood pressure monitoring accuracy in children with CHD will depend on the presence of arterial tree malformations and anatomic alteration by previous surgical corrections. For example, a modified Blalock–Taussig shunt or left subclavian flap procedure for CoA repair may render the blood pressure reading in the respective extremity inaccurate or difficult to obtain. Before CoA repair, lower-extremity blood pressure readings will differ from upper extremity pressures.

Postoperative Management of Children With CHD

Hypoventilation or mildly decreased oxyhemoglobin saturation are particularly hazardous in children with CHD. After tracheal extubation, oxygen should be administered during transport to the PACU (or ICU) and gradually weaned based on the patient's clinical condition. In patients with single ventricle or stage I physiology, oxygen saturation should be titrated to 85% for fear of decreasing PVR, increasing pulmonary blood flow, and decreasing systemic blood flow. Postoperatively, an anesthesiologist or intensivist familiar with their specific cardiac disease should follow these children closely. Analgesics and commonly used antiemetics are well tolerated in children with CHD.

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Suggested Readings

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4

Respiratory Diseases

LAURA PETRINI AND RONALD S. LITMAN

Upper Respiratory Infection

Upper respiratory infection (URI) is common in children presenting for anesthesia and the most common infection overall in children. The average child will have 6 to 8 URIs per year. Thus, it is important to understand the pathogenesis, clinical features, risk stratification, and anesthetic management of children with a URI.

URIs are almost always viral. Rhinoviruses are the most common, but influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, and coronavirus are also seen. Although the specific virus can be identified by laboratory testing, this is rarely performed.

Viral transmission most commonly occurs via mucosal contact from hands contaminated with infectious material, inhalation of airborne particles, or droplet contact with mucosa (e.g., sneezing). For this reason, patients with a URI will likely be on both contact and droplet type precautions when hospitalized, mainly to protect staff. Symptoms are caused by the child's immune response to the virus. For example, the influx of polymorphonuclear (PMN) cells in response to cytokine signals results in increased nasal secretions.

The symptoms of a URI vary based on the age of the patient and the specific virus. Most commonly, patients will present with nasal congestion, rhinorrhea, cough, and sneezing. Fever is less common (reported in approximately 15% of cases) and, if persistent, may be the sign of a bacterial infection such as otitis media, *Streptococcal* tonsillitis, or pneumonia. The color of nasal secretions is not indicative of severity of infection; rather, color is dictated by the number and activity of the PMN cells in the immune response.

A current or recent URI increases the risk for a perioperative respiratory adverse event (PRAE). These events range from benign coughing to serious laryngospasm, bronchospasm, or hypoxia that results in the need for escalation of care. Some clues to the risks of URI can be gleaned by the results of a 2010 study[1] in over 9000 patients. A positive respiratory history (nocturnal dry cough, wheezing during exercise, wheezing more than three times in the past 12 months, or a history of present or past eczema) in a child with a URI was associated with an increased risk for intraoperative bronchospasm, laryngospasm, and perioperative cough, desaturation, or airway obstruction. In addition, a history of at least two family members having asthma, atopy, or smoking increased the risk for PRAEs.

The risk for a PRAE decreases with time after initial infection, although controversy exists about the duration of time required for reduction of risk (ranging from 2 to 6 weeks). Because of this uncertainty, there is also no consensus when to schedule elective surgery after an acute URI. In a 1979 publication[2] that described the development of lower respiratory symptoms during general anesthesia in children with a URI, McGill and colleagues from National Children's Hospital wrote: "the optimal period of recovery from the URI that should be allowed before considering the patient a candidate for an elective surgical procedure has not been defined." More than 40 years later, this is still true. Subclinical pathology, such as airway edema, atelectasis, and bronchial reactivity may remain for up to several weeks after the symptoms of the acute URI have resolved, depending on the specific type of viral agent. Three to 4 weeks seems to be a reasonable waiting time, but for many children this merely represents the period between successive infections.

With these possible complications in mind, when a child presents with a URI, it is intuitive that an elective procedure requiring general anesthesia should be canceled. But, because so many children have a concurrent URI at the time of their scheduled surgery and long-term negative outcomes have not been demonstrated, this decision process is complex. How should the anesthesia provider decide when to cancel an elective procedure in a child with a URI? First, one should assess the severity of the child's illness. The child with a runny nose without additional findings may be suffering from vasomotor or allergic rhinitis, which is usually not associated with perioperative airway complications. If it is likely that the illness is viral, one must then identify the factors that increase perioperative complications. These include the following:

- Significant coexisting medical disease (especially cardiac, pulmonary, or neuromuscular disease)
- History of prematurity
- Lower respiratory tract signs (e.g., wheezing, rales)
- High fever (>102 °F)
- Productive cough

- Major airway, abdominal, or thoracic surgery
- Parent is worried about proceeding
- Surgeon is worried about proceeding (That'll be the day!)

If any of these risk factors are present, it may be prudent to perform the procedure when the child is in better health.

On the other hand, there are a variety of additional factors that may influence your decision to proceed with surgery. The most common reason for proceeding with a case even though risk factors are present is the presence of a URI that will likely continue without surgical intervention. This occurs when children require adenoidectomy or myringotomy to relieve chronic middle ear fluid collections. Nonmedical factors that might sway you to proceed with the case are logistical family concerns, such as the parents taking a day off from work, difficulty obtaining day care, traveling a long distance at a great inconvenience, and so forth. Because outcomes are not proven to be worse after surgery in children with a URI, these factors may play a role in the decision of whether or not to proceed. Most children who present with a URI have neither extremely mild symptoms nor severe symptoms. For these in-between children we must use our judgment to determine the proper course of action based on what we believe is best for the child.

Racial identity may influence risk. In a 2018 publication[3] from the University of Texas, African American children were shown to have significantly higher odds of PRAEs compared with a Caucasian group.

For urgent or emergent procedures, a discussion with the patient and family about the risk for PRAEs is prudent. In these situations, surgery will often need to proceed because of the risk for delaying. To optimize the patient preoperatively, additional treatments can be considered including:

- Inhaled beta agonist therapy (e.g., albuterol) is useful in patients with a history of asthma, although may also be of benefit to those with no prior diagnosis who present with wheezing secondary to a URI.
- Anticholinergics (e.g., glycopyrrolate) can be given to dry secretions but their use has not been proven effective.
- Steroids are rarely beneficial for a simple URI, except when the patient is presenting with a concomitant asthma exacerbation.

The risk for a PRAE can be approximately determined by clues from the preoperative evaluation. A history of fever, increased work of breathing, productive cough, wheeze, shortness of breath, copious secretions, or lethargy are important symptoms that may increase risk. Passive exposure to cigarette smoke and a history of atopy are additional risk factors. On physical exam, a toxic appearance or abnormal lung sounds, such as wheezing or rales, are also important predictors of increased risk. Additional evaluation with imaging or laboratory information is rarely needed.

Anesthetic management of the child with an active URI should be tailored to minimize airway irritability. Administration of a neuromuscular blocker to facilitate tracheal intubation will prevent laryngospasm. Humidification[4] of airway gases may prevent the thickening of secretions that is commonly encountered in these children. Some authors suggest administration of an anticholinergic agent, such as atropine or glycopyrrolate, to attenuate vagally mediated airway complications; however, this remains untested.

The anesthesiologist should also carefully consider the appropriate type of airway management based on the patient's history and the surgical procedure. When possible, airway instrumentation and placement of an endotracheal tube should be avoided as multiple studies have shown an increased risk for PRAEs (bronchospasm, desaturation, cough, and breath holding) in these patients. A natural airway or use of a laryngeal mask airway may decrease risk, but even LMA placement may be associated with complications in children with a URI.[5] Ventilation should be carefully tailored with judicious positive end–expiratory pressure (PEEP) to avoid the development of atelectasis. Anesthesia providers should expect PRAEs such as bronchospasm or laryngospasm and be prepared to treat these immediately.

In infants and children with a URI, apneic oxygenation is less effective; thus, oxyhemoglobin desaturation may occur faster than usual during rapid sequence induction when the child may not be receiving positive-pressure ventilation.

Postoperatively, the majority of patients with a URI will have an uneventful recovery without need for additional respiratory management. Patients with underlying pulmonary or cardiac comorbidities, however, are at higher risk for PRAEs.

Transient postoperative hypoxemia, postintubation croup, and postoperative pneumonia are probably more likely to occur in children with a URI. Long-term complications and true outcomes are difficult to define and quantify and may not differ between normal children and those with a current or recent URI.

Asthma

Asthma, or reactive airway disease, is an acute-on-chronic inflammatory disease of both larger and smaller airways. With a prevalence of 8%, it is the most common chronic illness in children in the United States and in other resource-rich countries and is concentrated in urban geographic areas that have a predominantly African American or Hispanic population. There is a strong genetic component and a correlation to other allergic-type conditions such as seasonal allergies and eczema. The majority of children present early in life (80% by age 5), although the presentation is often earlier and more severe in children with underlying pulmonary conditions such as bronchopulmonary dysplasia or respiratory syncytial virus infection.

The pathophysiology of asthma consists of the classic triad of bronchial hyperreactivity, inflammation, and mucous secretion. Triggers such as inhaled allergens (e.g., dust, pet dander, pollen, etc.), viruses, smoke, exercise, or even administration of nonsteroidal antiinflammatory drugs (NSAIDs) result in activation of an immunoglobulin E-mediated and nonimmunologic response in the airway. Specifically, mast cells located in the airway mucosa

release mediators such as histamine, tryptase, leukotrienes, and prostaglandins that result in contraction of airway smooth muscle (i.e., bronchoconstriction). These mediators also result in the hypersecretion of mucous, infiltration of inflammatory cells, and airway edema. Because of the continued immune response with the infiltration of more and more inflammatory cells, the airway remains hyperreactive. In addition to the immune response, the parasympathetic nervous system also plays a role in maintaining airway tone; when activated because of histamine release or other stimuli such as inhaled cold air or airway instrumentation, increased parasympathetic output via the vagus nerve results in an intracellular signaling cascade and ultimately, bronchoconstriction. Depending on the type and duration of exposure to the trigger, and the patient's immune and parasympathetic responses, exacerbations of asthma can last for hours or days, some resolving spontaneously whereas others require aggressive medical therapy.

Clinically, patients with asthma classically present with wheeze because of the narrowing of their airways from dynamic bronchoconstriction. Children may also demonstrate a persistent cough (often worse at night) and dyspnea on exertion. During an acute exacerbation, marked respiratory distress occurs, which may include chest wall retractions and a prolonged expiratory phase secondary to lower airway obstruction. The degree of audible wheeze, which is directly related to the amount of airflow in the airways, can fluctuate during an acute exacerbation. As the severity of an asthma exacerbation worsens and bronchoconstriction increases, the degree of audible wheeze may first increase because of airway narrowing but ultimately can decrease as the severity of bronchospasm results in lack of air flow. Thus, lack of wheeze can actually be a sign of impending respiratory failure.

The treatment of children with asthma targets the underlying pathophysiology, specifically bronchoconstriction and the hyperactive airway immune response. For patients with known triggers such as allergens and irritants, avoidance is key. Further chronic treatments are stratified based of the frequency of symptoms (Table 4.1) and the type of treatment used (Table 4.2).

Acute exacerbations are managed with escalated use of beta-agonist therapy and addition of other classes of medications. Inhaled anticholinergics targeting the parasympathetic nervous system, such as ipratropium bromide, combined with beta-agonist therapy has been shown to decrease the rate of hospital admission and thus will often be used in the acute management of these patients. Systemic steroids (prednisone, methylprednisolone, or dexamethasone), given orally or IV, are used to dampen the underlying immune response and decrease airway inflammation, although the initial effect is delayed and not seen until several hours after administration. For severely ill children, other treatment modalities include IV magnesium sulfate (direct smooth-muscle relaxation secondary to inhibition of calcium uptake), IV or subcutaneous epinephrine (direct beta-agonist), IV or subcutaneous terbutaline (direct beta-agonist), IV ketamine (sympathomimetic bronchorelaxation), intubation with delivery of inhaled anesthetic agents (bronchodilation), and finally extracorporeal membrane oxygenation (ECMO) for the most severe life-threatening cases.

TABLE 4.1 Stratification and Treatment of Asthma Based on Symptom Frequency

Classification	Symptom Frequency	Treatment
Mild Intermittent	≤2 days/week or ≤2 nights/month	No daily treatment Short-acting bronchodilator as needed
Mild Persistent	>2 days/week but not daily or >2 nights/month	Inhaled steroid (low dose)
Moderate Persistent	Daily or 1 night/week	Inhaled steroid (low dose) plus long-acting inhaled beta agonist or Inhaled steroid (medium dose)
Severe Persistent	Continual or Frequent nighttime	Inhaled steroid (high dose)

Anesthetic Management of Children With Asthma

A thorough history and physical examination will inform the anesthesia provider about the child's current or recent control of their asthma and indicate their relative risk for complications.

We recommend focusing on the following preoperative details to estimate the child's current risk of receiving general anesthesia:

- What is the child's category of asthma severity (see Table 4.1)?
- When was the child's last exacerbation that required use of a rescue inhaler or treatment with oral steroids?
- How frequently do the exacerbations occur?
- What typically triggers the child's exacerbation (e.g., environmental allergens, URI, smoke, etc.)?
- Has the child ever been hospitalized for asthma and if so, when was the last hospitalization?
- Has the child ever required ICU admission for asthma or noninvasive support or tracheal intubation for an asthma exacerbation?

The physical examination should focus on detecting expiratory wheeze, a prolonged expiratory time, and the child's use of accessory muscles of respiration. A pulse oximetry reading less than 96% in room air should prompt additional evaluation.

TABLE 4.2 Treatment of Asthma Based on Drug Class

Drug Class	Examples	Mechanism of Action	Things To Remember
Beta-agonist	Albuterol (short acting) Salmeterol (long acting)	Relaxation of airway smooth muscle by direct activation of the beta-2 receptor	Most commonly used for acute exacerbations Can be given with a metered-dose inhaler (MDI) or nebulization
Inhaled glucocorticoid	Fluticasone Budesonide Beclomethasone Triamcinolone	Antiinflammatory effects	Part of the controller therapy for asthma Can have systemic effects
Leukotriene receptor antagonist	Montelukast	Interferes with the pathway of metabolism of arachidonic acid, thus blocking inflammation	
Mast cell membrane stabilizer	Cromolyn	Prevents release of inflammatory mediators	Decreases the likelihood of acute exacerbations
Methylxanthine	Theophylline	Causes bronchodilation by inhibiting phosphodiesterase	Very narrow therapeutic range and safety concerns Fallen out of favor for chronic asthma management

Based on the information gathered in the history and physical examination, the anesthesia provider must determine whether the patient is appropriate for an elective procedure. If the patient does not appear to be optimized for elective surgery, they should be rescheduled at a later date. Optimized, however, does not necessarily mean that the child is symptom free. For example, mild wheezing may be serious in a child who never wheezes between acute exacerbations, as opposed to the child who continually has a baseline wheeze, and is considered to be optimized at the time of surgery. Preoperatively, the patient should be continued on all asthma medications. Prophylactic inhaled beta-agonists should be considered, given both at home before arrival and in the preoperative period.

The anesthetic management of children with asthma[6] is primarily aimed at preventing PRAEs. Bronchoconstriction may be triggered by airway manipulation; if possible, a face mask or supraglottic airway is preferred. If tracheal intubation is required, a cuffed endotracheal tube will facilitate higher peak inspiratory pressures should bronchospasm develop. Before tracheal tube placement, airway reflexes should be suppressed with a sufficiently deep level of general anesthesia. All inhaled anesthetic agents will accomplish this goal, in addition to providing direct bronchodilation. Desflurane should be avoided because of its irritative effects on the upper and lower airways. Propofol decreases respiratory events when used during induction, and in adults, propofol is associated with less bronchospasm than etomidate. Ketamine is also frequently used in asthmatic patients because of its ability to cause bronchodilation by releasing endogenous adrenergic agonists, but there appears to be no advantage over propofol. Use of neuromuscular blockade has been shown to reduce the risk of perioperative respiratory events, although caution must be used to avoid those that cause histamine release (e.g., atracurium). Similarly, some opioids (e.g., morphine) are associated with histamine release.

Regional anesthesia is encouraged as an alternative or supplement to general anesthesia in patients with asthma. Although regional anesthesia alone eliminates the use of airway manipulation, it is rarely feasible in younger children. Blunting of the sympathetic response as a result of central regional blockade is not likely to initiate or exacerbate bronchospasm in an asthmatic child because there is no direct adrenergic innervation to human airway smooth-muscle.

Artificial ventilation may differ in children with asthma because of the inherent obstructive physiology in these patients. The anesthesiologist should ensure an appropriate expiratory time to allow for adequate exhalation and prevent breath stacking, which may result in air trapping and hyperinflation. Obstruction will be evident on capnography as a delayed or up-sloping rise of the end tidal carbon dioxide tracing. The ventilation strategy should be modified by decreasing minute ventilation (decreasing respiratory rate or tidal volume) with resultant permissive hypercapnia, or reducing the inspiratory/expiratory ratio to allow for more time for complete exhalation.

Children with preexisting asthma do not often develop exacerbation of their disease during an anesthetic. When it does, bronchospasm often presents as wheezing, increased peak inspiratory pressures, decreased tidal volume, obstructive pattern on capnography, and oxyhemoglobin desaturation. The anesthesiologist should first rule out other causes of that constellation of signs. The circuit and endotracheal tube should be checked to be sure there are no obvious obstructions, including kinks or mucous plugs. Endotracheal tube depth should be assessed and breath sounds confirmed to ensure lack of caudad tube migration (main bronchial intubation) or pneumothorax. If upon further investigation bronchospasm is still assumed, several steps in management should occur simultaneously. First, the patient should be transitioned to 100% inspired oxygen. Next, assuming hemodynamic stability, the anesthetic

• **Fig 4.1.** The albuterol canister is placed within the barrel of a 60-mL syringe, which is connected directly to the elbow in the breathing circuit. The plunger of the syringe is used to actuate the canister. (Photo credit to Ronald S. Litman)

should be deepened by administering an intravenous agent such as propofol or increasing the concentration of inhaled agent. Often, the deepening of anesthesia will be sufficient to resolve the episode of bronchospasm, which is frequently secondary to stimulation of the tracheal mucosa during a period of light anesthesia.

When bronchospasm is not amenable to deepening the anesthetic, further bronchodilatory strategies are warranted. The first line treatment is administration of an inhaled beta-agonist. Practically, this can be accomplished intraoperatively by using a metered-dose inhaler connected to the anesthesia breathing circuit between the inspiratory limb and patient Y-piece (Fig. 4.1). This is performed by inserting the drug canister into a 60 mL syringe barrel and using the plunger to actuate the medication, or by directly inserting the canister into the breathing circuit using a specialized adapter (Fig. 4.2, Medicomp, part 1423, Princeton, MN 55371). Access into the circuit is attained through a removable cap, through which the spray is actuated just before a positive-pressure breath. In practice, however, a very low percentage of the bronchodilator actually reaches the lungs[7] because of adherence to the circuit and endotracheal tube. The smaller the diameter of the endotracheal tube, the less actuated medication will actually reach the lungs. Therefore, multiple administrations of albuterol are delivered (usually between 10 and 20) until bronchospasm is relieved, or until the patient develops tachycardia from absorption of the adrenergic agonist. Conversely, an infusion of low-dose epinephrine can also be used for refractory bronchospasm.

Cystic Fibrosis

With a frequency of approximately 1 in 3000 live births, cystic fibrosis (CF) is the most common fatal autosomal recessive disease in Caucasians. The disease can occur because of any of more than 2000 pathogenic variants in the cystic

• **Fig 4.2.** The albuterol canister is connected to the breathing circuit via a specialized adaptor and actuated by pushing on the bottom of the canister.

fibrosis transmembrane conductance regulator (CFTR[8]) gene, which encodes a regulatory protein found in exocrine tissue. Because of the vast number of possible mutations, many individuals are carriers for the disease, with frequencies as high as 1 in 25 in some Caucasian populations. The most common pathogenic variant in the Northern European Caucasian population and the United States is F508del, accounting for up to 90% of patients with CF.

The CFTR gene is located on the long arm of chromosome 7 and codes for an ion channel which transports chloride ions down the electrochemical concentration gradient across epithelial cell membranes. When chloride ions move across the cell membrane, sodium ions follow passively to counterbalance the ionic charge. This results in an increased electrolyte concentration, which in turn draws water by osmosis. When the gene is altered, the ion channel is unable to conduct chloride ions appropriately, resulting in abnormalities in water movement. Without this water, secretions become thick and viscous which limits clearance and causes progressive obstruction. Static insipid secretions create a prime culture medium for bacteria, leading to bacterial colonization and overgrowth with chronic inflammation and destruction of extracellular architecture. Multiple organs contain the CFTR protein, including the respiratory tract, pancreas, liver, gallbladder, intestine, and reproductive tract.

This pathophysiology leads to a variety of clinical manifestations that take the form of a chronic life-threatening illness throughout an affected person's life. Patients often present with cough in early childhood because of difficulty clearing secretions. As the build-up of secretions results in smaller and then larger airway blockage, further symptoms such as atelectasis, bronchospasm, pneumothoraces, and frequent antibiotic-resistant bacterial infections occur. Chronic hypoxia may result in clubbing of the digits and right-heart failure. Destruction of the architecture of the respiratory tree puts patients at risk for bronchiectasis and hemoptysis, which can cause anemia. Pansinusitis and nasal polyps are common. In the gastrointestinal tract, thickened secretions result in large malabsorptive stools. This can present in the newborn period as a meconium ileus. Older children may have constipation, vomiting, and abdominal distention. Pancreatic insufficiency occurs in about two-thirds of CF patients from birth and about 85% into adulthood. This results in malabsorption and fat-soluble vitamin (A, D, E, and K) deficiencies. Progressive pancreatic insufficiency results in bouts of pancreatitis and islet cell damage, which leads to abnormal glucose homeostasis and diabetes mellitus.

The diagnosis of CF is confirmed by history, physical examination, and laboratory analysis. In the United States, all newborns are tested for CF in the routine newborn screen. If positive, the child is referred for further testing with either a sweat test (elevated sweat chloride levels are a diagnostic hallmark) or genetic testing. Children with confirmed CF are followed with periodic chest radiographs, pulmonary function tests, and blood markers consistent with the pathophysiology of the disease (e.g., glucose and Hb A_{1c} for endocrine pancreatic function, prothrombin time for signs of vitamin K deficiency, sputum cultures for bacterial overgrowth, etc.).

Medical management of CF improves continuously, and patients now often live well into adulthood. Treatment strategies include chest physiotherapy, exercise, and frequent coughing to mobilize secretions. Bronchodilators and antiinflammatory medications decrease airway reactivity. Bacterial pneumonia requires aggressive antibiotic therapy. Nebulized hypertonic saline and dornase (Pulmozyme) break down thick DNA complexes that accumulate in mucus from cell destruction and bacterial infection. Normal growth is often achieved with pancreatic enzyme replacement, fat-soluble vitamin supplements, and high-calorie high-protein diets.

Common reasons that children with CF require surgery include meconium ileus in the newborn period, intestinal obstruction, nasal polypectomy, and endoscopic sinus surgery. Older or more severely ill children may require anesthesia for placement of indwelling central line access or gastrostomy tube insertion. Preoperative evaluation of pulmonary function may include chest radiography or pulmonary function tests; arterial blood gas analysis is rarely useful. Optimization of infection control and physiotherapy for secretion clearance are priorities and should be coordinated with the child's pulmonologist.

There is no best anesthetic technique for patients with CF. Some advocate use of ketamine because of its minimal effects on ventilatory function; however, others cite ketamine's ability to increase airway secretions. Some pediatric anesthesiologists prefer a liberal fluid strategy to decrease viscosity of bronchial secretions while others advocate minimization of fluids to decrease airway secretions at the expense of increased viscosity. It seems that avoidance of either overhydration or dehydration is the most prudent course of action. There are no modern clinical studies on anesthetic management of children with CF.

In children with significant pulmonary disease and poor nutritional status, placement of an endotracheal tube and application of mechanical ventilation often entails postoperative transfer to the ICU and the difficult decision-making process concerning the timing and appropriateness of tracheal extubation. Postoperative management should be proactively planned in conjunction with the intensive care physicians and with the input of the patient and family. When possible, the least invasive form of ventilatory support should be chosen.

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5

Neurologic and Neuromuscular Diseases

JAY GARCIA AND RONALD S. LITMAN

Cerebral palsy and seizure disorders are very common in the pediatric population, thus anesthesia providers should be familiar with their clinical characteristics and the pharmacologic agents used for their treatment. Although less common, myopathies are associated with significant morbidity in children, and are noteworthy because of their potential association with malignant hyperthermia and the potentially catastrophic[1] hyperkalemic response to administration of succinylcholine (and in some cases, volatile anesthetics).

Cerebral Palsy

Cerebral palsy (CP) is a static motor encephalopathy that affects tone, coordination, and movement of the musculoskeletal system. It is a collection of motor system disorders caused by perinatal or early childhood neurologic insult. The cumulative incidence rate of CP at the age of 5 to 7 years is 2.4 cases per 1000 live births. The contribution of very low birth weight infants to this population of children is significant: about 52,000 very low birth weight infants (<1500 g) are born annually. These infants make up more than 25% of children diagnosed with CP.

Children with CP exhibit a wide variety of clinical manifestations that range from mild (e.g., slight lower extremity spasticity and normal cognitive function) to severe (e.g., spastic quadriplegia and marked intellectual disability). Respiratory system dysfunction usually parallels the overall severity of the disease. Bulbar motor dysfunction causes a loss of airway protective mechanisms (impaired cough, gag, etc.) and leads to chronic pulmonary aspiration, recurrent pneumonia, reactive airway disease, and parenchymal lung damage. Other airway considerations include abnormal dentition, temporomandibular joint dysfunction, and positioning difficulties. Gastrostomy tubes are often placed during infancy to optimize nutritional status.

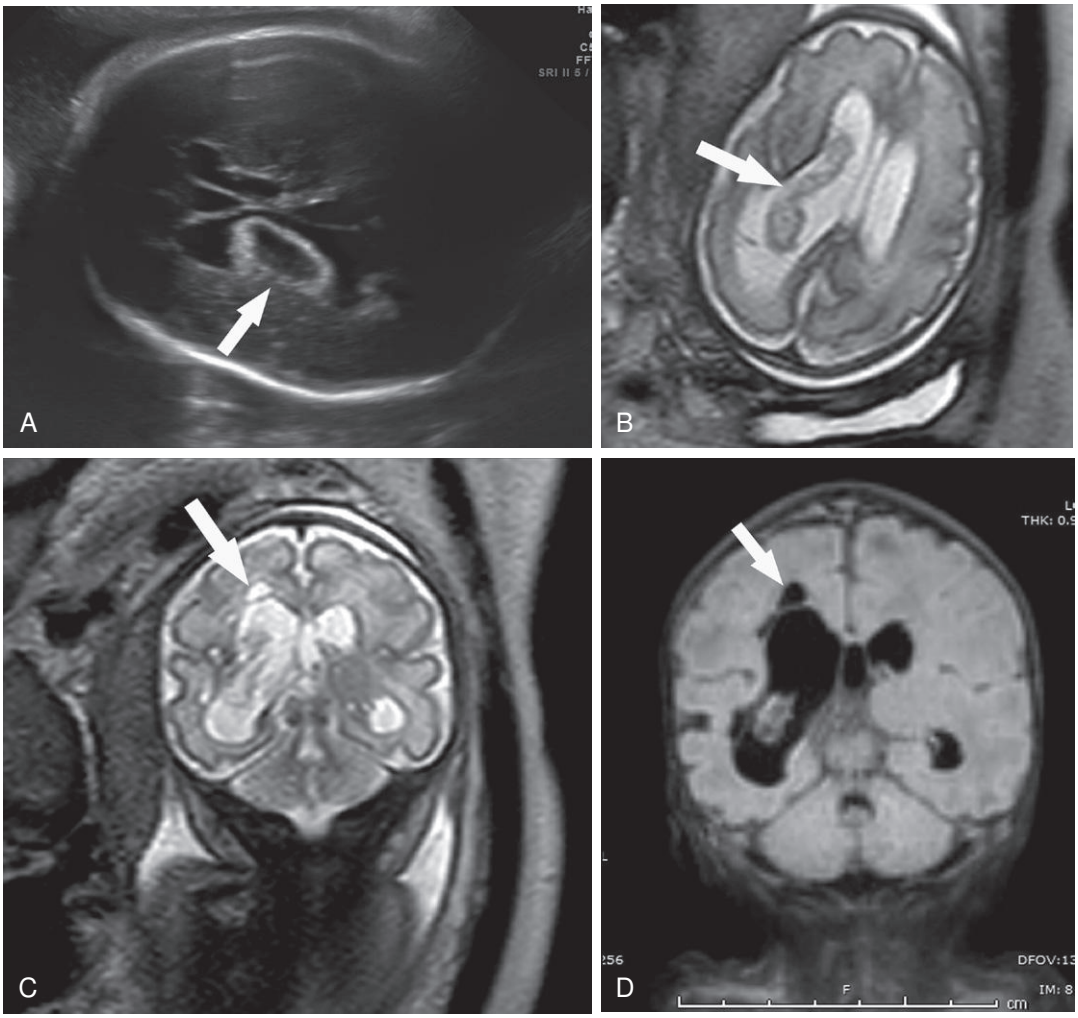
Prematurely born infants may develop areas of brain ischemia secondary to cerebral hemorrhages in the early newborn period. The area of infarction is termed *periventricular leukomalacia* (white matter atrophy surrounding the ventricles) and is associated with development of varying degrees of limb spasticity (Fig. 5.1).

Chronic absence of motor input results in progressive development of limb contractures during childhood that worsen with age. Baclofen, a gamma-aminobutyric acid (GABA) agonist, reduces pain associated with muscle spasms and slows development of contractures. Side effects are common with oral baclofen,[2] thus intrathecal baclofen has become popular for children of any age.[3] This requires surgical intervention for catheter placement and implantation of the baclofen pump in the anterior abdominal wall. Side effects of baclofen include urinary retention and lower extremity weakness, which usually abate when the dose is reduced. Abrupt withdrawal from oral or intrathecal baclofen may cause seizures, hallucinations, disorientation, and dyskinesias, and when severe may be fatal. If intrathecal baclofen is discontinued because of infection of local structures or cerebrospinal fluid (CSF), close observation of the patient for withdrawal symptoms is necessary. On occasion, when withdrawal is severe enough, a temporary intrathecal catheter may be placed to provide baclofen. Two case reports[4,5] highlight the successful use of dexmedetomidine to manage acute, severe withdrawal in two patients.

Children with CP may undergo various surgical interventions during childhood. Orthopedic procedures are the most common and include scoliosis repair and a variety of limb procedures to improve range of motion and decrease progression of contractures. Dorsal rhizotomy may be required to control painful lower limb spasticity. Nissen fundoplication is performed to control chronic gastroesophageal reflux and may include a feeding gastrostomy, which is increasingly performed by laparoscopy.

Surgical complications are relatively common. In a review of 19 children[6] with CP undergoing scoliosis surgery, 9 had at least one major complication, most commonly blood loss or the need for postoperative mechanical ventilation. Risk factors included the presence of two or more comorbidities and thoracotomy.

Preoperative assessment includes defining and optimizing all systemic medical illnesses. Concurrent upper



• **Fig 5.1.** Periventricular leukomalacia. (A) Axial fetal ultrasound through the brain shows enlargement of the right choroid plexus (arrow). (B) Axial fetal magnetic resonance imaging shows blood products within the choroid plexus (arrow). (C) Coronal T2-weighted, and (D) coronal FLAIR images show cystic lesions in the periventricular region (arrow) consistent with periventricular leukomalacia. (From Berlin, Sheila C, Meyers Mariana L. Neonatal imaging. In: *Klaus and Fanaroff's Care of the High-Risk Neonate*. 18th ed. Elsevier; 2020:409–436.)

respiratory infections are poorly tolerated and will exacerbate preexisting respiratory disease. Preoperative anxiolysis should be administered to children when appropriate, although some children with CP are prone to upper airway obstruction with mild sedation and should be closely monitored. Administration of an anticholinergic agent may decrease pooling of oropharyngeal secretions, but this is not evidence-based. Routine preoperative echocardiography for cardiovascular evaluation in the absence of signs or symptoms suggestive of cardiac dysfunction is not necessary.[7]

There are no special considerations when choosing an agent for induction or maintenance of general anesthesia because children with CP usually tolerate all anesthetic agents well. If a gastrostomy tube is present, suctioning or leaving it open before induction of general anesthesia may help decompress the stomach. Because of possible malformation of facial structures, mask ventilation may be difficult, but endotracheal intubation should be straightforward in most cases. Presence of gastroesophageal reflux and increased oropharyngeal secretions may encourage the anesthesia provider to secure intravenous (IV) access earlier during induction of anesthesia and secure the airway using IV induction agents.

Children with CP demonstrate increased sensitivity to succinylcholine[8]; approximately 30% of children with CP have abnormal distribution of acetylcholine receptors. Succinylcholine-induced hyperkalemia in CP has not been studied to the extent that is required to capture such a rare event. We are aware of a child with CP that experienced cardiac arrest upon receiving succinylcholine; therefore, succinylcholine should be used only to treat life-threatening airway emergencies in CP patients. Nondepolarizing muscle relaxants are less potent and have a relatively shorter duration of action in children with CP. This may be related to chronic anticonvulsant administration or underlying spasticity.

Sevoflurane is relatively more potent (i.e., lower minimum alveolar concentration) in children with CP. Increased opioid sensitivity should be assumed in all but mild forms of CP. Doses should be reduced, and greater vigilance at the

time of extubation is necessary to ensure the child's ability to maintain a patent upper airway. Hypothermia is a common intraoperative problem in children with CP. Impaired temperature regulation is caused by hypothalamic dysfunction and the relative absence of muscle and subcutaneous fat. A child with spastic quadriplegic CP may have an esophageal temperature of 34°C to 35°C within a few minutes of induction of anesthesia. Therefore the ambient temperature should be 21°C to 24°C (70°F–75°F) in the operating room while the patient is relatively exposed during induction and line placement. Line placement will also become increasingly more difficult as the child becomes increasingly hypothermic. Forced-air warming is effective and should be used starting in the preoperative holding area, if possible.

Regional analgesia may benefit children with CP who have difficulty communicating the severity of their pain. Epidural catheter placement via lumbar or caudal approach is commonly used for lower extremity orthopedic procedures. Addition of epidural clonidine[9] to local anesthesia may help reduce postoperative lower limb spasticity, which can be a significant component of their postoperative discomfort. Oral diazepam[10] may help alleviate muscles spasms.

Seizures are present in about 30% of patients with cerebral palsy. Anticonvulsants should be continued until the morning of surgery and reinstituted as quickly as possible during the postoperative period. When it is not feasible to continue enterally administered anticonvulsants, some can be administrated rectally (phenytoin, valproic acid, carbamazepine, levetiracetam) and some intravenously (phenytoin, valproic acid, phenobarbital, levetiracetam). If the surgical procedure causes significant blood loss, anticonvulsant levels should be checked postoperatively, and doses should be adjusted to reestablish optimal levels.

Seizure Disorders

Seizures are clinical manifestations of a variety of disorders. Febrile seizures are the most common type, affecting 5% of children. Idiopathic epilepsy, primarily seen in older children, is less common with an estimated incidence of 0.6% of the population. Trauma, hypoxia, and infection are the primary pathologic causes of seizures in infants. Additional causes include metabolic disease, hypoglycemia, electrolyte abnormalities, toxic ingestions, and congenital or developmental defects. However, in about 50% of children, the etiology of the seizure is unknown.

The currently accepted international classification[11] of epileptic seizures divides these disorders into three etiologic categories and three types of seizures (Table 5.1). Etiologic categories include genetic, structural/metabolic, and unknown. Seizure types are divided by onset location: focal, generalized, or unknown.

Focal onset seizures are akin to partial seizures, in which the initial clinical and electroencephalogram (EEG) changes indicate activation of a system of neurons limited to part of one cerebral hemisphere. Focal seizures may or may not have impaired awareness. Focal seizures can be subdivided by clinical presentation and EEG characteristics into motor, sensory, autonomic, or higher cortical/aura symptoms. There may not be a postictal state. Focal onset seizures may spread bilaterally and progress to a "focal to bilateral" tonic-clonic seizure.

TABLE 5.1 International Classification of Seizures

Focal Onset Seizures
• Aware or impaired awareness • Motor onset or non motor onset • Focal to bilateral tonic-clonic
Generalized Onset Seizures

• Motor
  • Tonic-clonic
  • Other motor
• Non motor (absence)

Unknown Onset Seizures

• Motor
  • Tonic-clonic
  • Other motor
• Non motor (absence)
• Infantile spasms (West syndrome)
• Unclassified Seizures

Generalized onset seizures involve bilateral cerebral hemispheres with clinical and EEG changes from the onset and accompanied with impaired awareness. Motor manifestations, if present, are also bilateral. Generalized seizures may be convulsive or nonconvulsive.

Generalized tonic-clonic seizures consist of an initial tonic contraction phase, during which it is common for patients to become apneic and cyanotic from the tonic rigidity of the thoracic cavity. This is followed by the clonic, repetitive twitching phase, where breathing resumes but can be shallow and irregular.

Nonmotor "absence" seizures are nonconvulsive generalized seizures. They are further subdivided into typical (staring spells during which the patient is not responsive, and last a few seconds), atypical (less abrupt onset/offset, some loss of muscle tone), myoclonic, or eyelid myoclonia.

Motor seizures are subdivided by the presence or absence of three characteristics:

1. Tone
2. Clonus (regular and rhythmic twitch)
3. Myoclonus (irregular, arhythmic)

Generalized motor seizures range from **atonic** (where atonia is the only prominent feature) to **myoclonic-tonic-clonic** (where all three abnormalities are alternatively present).

Epileptic spasms, which include infantile spasms, are of poorly understood origin and classified as "unknown."

Infantile spasms (West syndrome) consist of the triad of unique salaam-like seizure movements, arrest of psychomotor development, and a characteristic EEG pattern called

hypsarrhythmia. The onset peaks between 4 and 7 months of age and almost always occurs before 12 months. It can be associated with a known underlying neurologic disorder, or it can be idiopathic and associated with a poor neurodevelopmental outcome. Lennox-Gastaut syndrome consists of different types of seizures that occur frequently and are difficult to control. It manifests itself in the 3- to 5-year age group and is associated with severe intellectual disability. Both infantile spasms and Lennox-Gastaut syndrome are difficult to control with anticonvulsant agents.

Anesthetic concerns for children with seizure disorders depend on coexisting morbidities and are individualized depending on the mental status of the child. If necessary, children who require strict pharmacologic control of their seizure disorder should have their oral anticonvulsants converted to the IV forms (or equivalent medications if IV forms are not available) during the preanesthetic fasting interval and during the postoperative period if oral intake is not possible. In most cases, preanesthetic anticonvulsant levels are not necessary. Anesthesiologists should be aware of the most common side effects of anticonvulsants.[12]

Most anesthetic and analgesic agents can be safely administered to children with seizure disorders. A possible exception is multiple doses of meperidine. Its metabolite, normeperidine, possesses proconvulsant properties. Nitrous oxide, sevoflurane, etomidate, propofol, and all opioids have been anecdotally associated with seizure-like movements or lowering of the seizure threshold[13] in both healthy and epileptic patients, without serious sequelae. In most of these cases these movements were a benign form of myoclonus. Virtually all general anesthetic agents except ketamine have anticonvulsant properties in doses associated with loss of consciousness but lower doses have been associated with an increase in EEG spike activity.[14] Higher doses and shorter dosing intervals of neuromuscular blockers are required in patients taking anticonvulsants. The precise mechanism of this is unknown. However, this resistance is not as prominent for neuromuscular blockers that are metabolized in the plasma (i.e., atracurium), so it may be related to a pharmacokinetic effect based in the liver. Levetiracetam may prolong neuromuscular blockade. Anticonvulsants may also cause some resistance to opioids. Although definitive data are lacking, it does not appear that general anesthesia impacts the postoperatively subsequent frequency or severity of seizures.

Neuromuscular Diseases

Neuromuscular diseases can be broadly divided into disorders of the muscle or of neuromuscular transmission (Table 5.2). Muscle diseases can be further categorized into developmental myopathies, muscular dystrophies, and metabolic myopathies. Disorders of neuromuscular transmission can be further categorized into diseases of the neuromuscular junction and diseases of anterior horn cells. This list is extensive and only the most common and most important in pediatric anesthesia will be reviewed here.

TABLE 5.2 Classification of Neuromuscular Diseases of Childhood

Muscle Diseases
Developmental
• Nemaline myopathy
• Central core myopathy
• Myotubular myopathy
Muscular Dystrophies
• Duchenne muscular dystrophy
• Becker muscular dystrophy
• Myotonic dystrophy
• Limb-girdle muscular dystrophy
• Facioscapulohumeral muscular dystrophy
• Congenital muscular dystrophy
Metabolic Dystrophies
• Potassium-related periodic paralysis
• Glycogenoses
• Mitochondrial myopathies
• Lipid myopathies
Diseases of Neuromuscular Transmission
Neuromuscular Junction Disorders
• Myasthenia gravis
• Organophosphate poisoning botulism
• Tick paralysis
Anterior Horn Cell Diseases
• Spinal muscular atrophy (SMA)
• Poliomyelitis

Muscle diseases, or myopathies, are characterized by muscle weakness and atrophy. Many children are symptomatic at birth, although others are normal in early infancy only to develop weakness in the first few years of life. The myopathies are of interest to anesthesiologists for two major reasons. First, some are associated with an increased risk for malignant hyperthermia; second, all myopathies have at least a theoretical risk for developing life-threatening hyperkalemia after administration of succinylcholine (and, rarely, inhalational anesthetics). Children with myopathies often require multiple surgical procedures throughout childhood. These include a muscle biopsy as a component of the diagnostic workup, insertion of a gastrostomy or tracheostomy as weakness worsens, and a variety of orthopedic procedures for alleviation of contractures and scoliosis. A retrospective 20-year review[15] of 877 consecutive neuromuscular disorder patients undergoing muscle biopsies found no incidents involving hyperkalemia or malignant hyperthermia (MH), providing further evidence of the rarity of these events and of the safety of modern anesthetics.

As with neurologic diseases, anesthetic considerations for children with muscle diseases[16] largely depend on the medical condition of the child because there is a wide spectrum of affliction, even between children with the same diagnosis. Although only central core disease and a handful of other rare ryanodine receptor-related myopathies have been genetically linked to MH,[17] many pediatric anesthesiologists choose a nontriggering anesthetic technique for all

children with myopathies. Use of nondepolarizing muscle relaxants depends on the baseline strength of the child. Careful titration of the neuromuscular blocker based on train-of-four monitoring is recommended. Children with muscle weakness are at increased risk for requiring postoperative mechanical ventilation; therefore, this possibility should be proactively addressed with the parents and child if appropriate.

Developmental Myopathies

The developmental myopathies consist of a heterogeneous group of congenital myopathies that are mostly nonprogressive, although some patients show slow clinical deterioration. Most of these conditions are hereditary, but some are sporadic. These include nemaline rod myopathy, central core disease (CCD), and myotubular myopathy. CCD is an autosomal dominant disease characterized by hypotonia and proximal weakness at birth. Unlike other muscle diseases, there appears to be a predisposition of CCD patients to malignant hyperthermia susceptibility in the form of a pathogenic variant for the ryanodine receptor on chromosome 19 (*RYR1*). However, the literature is conflicting, and the subject of myopathies and MH susceptibility continues to evolve. However, any patient with a myopathy associated with an *RYR1* pathogenic variant should be considered MH susceptible. Current best practices[18] favor regional anesthesia whenever possible, supplemented with total intravenous anesthesia. Inhaled anesthetics are considered safe in conditions not associated with MH susceptibility, such as mitochondrial myopathy. Most important, in all myopathic patients is attention to the cardiopulmonary system, the degree of muscular paralysis, and the core temperature. When significant muscle atrophy is present, these children are predisposed to hypothermia and hypoglycemia.

Muscular Dystrophies

Although the muscular dystrophies are a group of unrelated disorders, there are four obligatory criteria that distinguish them from other neuromuscular diseases:

1. They are primary myopathies.
2. They have a genetic basis.
3. Their course is progressive.
4. Degeneration and death of muscle fibers occur at some stage in the disease.

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease that, although present at birth, usually presents in early childhood as weakness and motor delay. Additional clinical manifestations include pseudohypertrophy of the calves and elevated baseline creatine phosphokinase. Because weakness is greatest in the proximal muscle groups, the child must rise from the sitting position in two steps: first leaning on the hypertrophied calves and then pushing the trunk up with the arms. This is referred to as *Gower sign* and is nearly pathognomonic for DMD. Eventually, progressive and severe muscle atrophy and weakness cause loss of the ability to ambulate. The most serious aspects of DMD include a progressive cardiomyopathy and respiratory failure secondary to ventilatory pump failure. A retrospective review[19] of 12 DMD patients who underwent gastrostomy found that 9 had a forced vital capacity ≤36% of predicted, with 8 being dependent on non-invasive positive pressure ventilation (NIPPV). Cognitive abnormalities are usually mild, if present at all. Most children become wheelchair-bound early in the second decade, with death in early adulthood from either respiratory failure or cardiomyopathy.

Adverse myocardial changes arise before overt cardiac dysfunction, and guidelines[20] recommend yearly cardiac screening beginning at diagnosis. Anesthesiologists are involved in the multidisciplinary consideration[21] and approach to left ventricular assist device (LVAD) placement, implantable cardioverter-defibrillator (ICD) placement, or heart transplantation in patients with advanced cardiac dysfunction.

Although there is no genetic link to MH susceptibility for these patients, many pediatric anesthesiologists perform a nontriggering technique because of the increased risk for rhabdomyolysis upon exposure to succinylcholine or inhaled agents. Some authors refer to it as *anesthesia-induced rhabdomyolysis*. However, careful use of inhaled agents for a relatively short period of time to secure an IV line is likely safe. Nondepolarizing muscle relaxants should be used with caution: administration of rocuronium to patients with DMD results in a delayed time to onset and delayed time to recovery. Use of succinylcholine in dystrophinopathies is contraindicated because of the risk for life-threatening hyperkalemia. A word of caution: there exists a report of a child[22] with DMD who had a stable cardiovascular profile preoperatively but unexpectedly developed acute heart failure when exposed to a propofol-sufentanil anesthetic for spinal fusion.

A less severe (yet debilitating) disease is Becker-type muscular dystrophy. Similar features to DMD include calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of CK. However, the onset of weakness in Becker-type dystrophy is later in life than with DMD, and death usually occurs at a later age than with DMD. The anesthetic considerations are identical to those for DMD. Life-threatening rhabdomyolysis has been reported immediately after isoflurane anesthesia.

Spinal Muscle Atrophy

Spinal muscle atrophy (SMA) is an inherited autosomal recessive disorder characterized by anterior horn cell degeneration and is found as one of three clinical syndromes. Type 1 (Werdnig-Hoffman, disease) is the most severe, beginning in early infancy. It is characterized by significant muscle weakness and atrophy, except for diaphragmatic sparing which occurs later in life. Type 2 (Dubowitz disease) presents between 6 and 12 months of age and has a more prolonged, slightly milder course. Type 3 (Kugelberg-Welander disease) is the least debilitating. Cognitive abilities

remain unaffected in all forms of the illness. Life expectancies vary with the severity of the disease and are improving with the emergence of targeted therapies; death occurs from repeated aspiration or lung infections.

As of 2016, there is a Food and Drug Administration (FDA)-approved treatment for SMA: intrathecal nusinersen.[23] Adverse events of intrathecal therapy such as headache and postlumbar puncture syndrome occur about 32% of the time and appear to be more common when the procedure involves older children, SMA type 3 patients, or larger (21- or 22-gauge) needles.

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Suggested Reading

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Gastrointestinal Diseases

REBECCA ISSERMAN, PETAR MAMULA AND RONALD S. LITMAN

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is a term used to describe a leaky lower esophageal sphincter that causes a child to regurgitate recently ingested meals. It is common in the first year of life, especially in children born premature, and usually resolves during early childhood. Children with GER related to neuromuscular disorders, such as cerebral palsy, will continue to reflux throughout childhood. Because of weakened airway protective mechanisms, these children often demonstrate chronic pulmonary aspiration that results in repeated episodes of pneumonitis and hypoxemia. Some children require a Nissen fundoplication, a surgical "tightening" of the lower esophageal sphincter, to prevent GER.

Many anesthesiologists assume that children with GER are at risk for pulmonary aspiration on induction of anesthesia and will opt for a rapid sequence induction. But to do so, an IV catheter must be placed preoperatively, which is not a routine procedure in many pediatric centers. This practice also obligates the placement of an endotracheal tube instead of a face mask or a supraglottic airway (SGA). No data exist to justify this practice. Studies that assessed residual gastric volumes after a normal preanesthetic fast have demonstrated no differences between children with GER and normal controls. The authors' opinion is that GER occurs only when there is food in the stomach of susceptible children. When these children are fasted normally, gastric volumes at induction of anesthesia are low and do not pose an increased risk for pulmonary aspiration.

There are additional valid reasons for not performing a rapid sequence induction in children with GER. First, the performance of cricoid pressure[1] reflexively decreases lower esophageal pressure, thus promoting passive regurgitation of gastric contents. Second, paralysis or relaxation of the cricopharyngeus muscle (a striated skeletal muscle) that forms the upper esophageal sphincter may allow passively regurgitated gastric contents to reach the larynx. Lastly, acid reflux into the lower third of the esophagus reflexively causes an increase in upper esophageal sphincter tone, which would not occur in the presence of neuromuscular blockade.

Inflammatory Bowel Disease

Inflammatory bowel disease[2] (IBD) primarily consists of Crohn disease and ulcerative colitis (UC). Crohn disease is a chronic inflammatory bowel disease that is seen in children and young adults, but it is also increasingly seen in very young children. (This "very early onset"[3] IBD is seen primarily in children with IBD associated with genetic syndromes.) Clinical manifestations, among others, include diarrhea, abdominal pain, rectal bleeding, anal fistulas, anemia, and weight loss. Extraintestinal manifestations include joint pain and swelling, growth failure, and delayed puberty. Therapy includes administration of 5-aminosalicylic acid (5-ASA) preparations, nutritional therapy, corticosteroids, immunosuppressants like methotrexate and 6-mercaptopurine, and biologic medications (i.e., monoclonal antibodies such as infliximab, vedolizumab, and ustekinumab).

Ulcerative colitis is characterized by inflammation of the large intestine that manifests clinically as abdominal cramping, diarrhea, and bloody stools. Associated systemic findings include anorexia, weight loss, low-grade fever, and anemia. Severe cases of colitis can result in severe anemia requiring blood transfusion, hypoalbuminemia, and toxic megacolon. Approximately 20% of cases of UC occur during childhood. As with Crohn disease, the primary therapeutic options are antiinflammatory therapy with 5-ASA preparations, corticosteroids, and biologic therapy, depending on disease severity.

Children with IBD require repeated esophagogastroduodenoscopies and colonoscopies during the course of their disease, for which general anesthesia is usually required. In Crohn disease surgery is indicated in select cases when medical therapy has failed. For example, when microperforations have resulted in a phlegmon, in cases of intestinal strictures which result in obstruction, or with perforation. Intestinal or colonic resections are palliative but not curative. Surgery is indicated for intractable colitis and toxic megacolon with peritonitis. Because UC is confined to the large intestine, colectomy is considered curative.

There are no unique anesthetic considerations for children with IBD. Anecdotal data indicate that these children require higher than usual amounts of opioids. This

may be related to tolerance from intermittent or chronic opioid use.

Neonatal Hyperbilirubinemia

Some neonates manifest jaundice in the first week of life. Unconjugated (indirect) hyperbilirubinemia[4] occurs because of the breakdown of fetal erythrocytes in combination with low activity of glucuronyl transferase, the enzyme responsible for conjugation of bilirubin to glucuronic acid. It manifests clinically as jaundice of the skin and sclera and is most prominent after the third day of life, especially in prematurely born infants and in term breast-fed infants. Concomitant medical disorders that cause hemolysis and contribute to hyperbilirubinemia in an additive fashion include hemolytic disease of the newborn, spherocytosis, G-6-PD deficiency, and presence of a cephalohematoma.

Treatment is indicated when serum bilirubin levels are excessively high. The potential for neurotoxicity of the developing brain (kernicterus) is historically associated with bilirubin levels greater than 20 mg/dL in full-term infants. Prematurity, hypoxemia, acidosis, and hypothermia increase the likelihood of kernicterus in the presence of hyperbilirubinemia. Phototherapy is the initial treatment; exchange transfusions are required in accelerated cases. Bilirubin values that trigger phototherapy or exchange transfusion vary between institutions.

Chronic Liver Disease

Chronic liver disease is associated with congenital biliary atresia for which a Kasai procedure or liver transplant is required. Other possible causes include α_1-antitrypsin deficiency, cystic fibrosis, tyrosinemia, and Wilson disease, among others. Clinical manifestations will depend on the remaining degree of liver function and will include ascites, portal hypertension (with esophageal varices), and coagulopathy. Respiratory insufficiency in children with advanced liver disease is caused by loss of functional residual capacity from the mass effect of ascites or hepatomegaly, and creation of intrapulmonary shunts (hepatopulmonary syndrome). Fulminant hepatic failure is associated with encephalopathy and increased intracranial pressure.

Principles of anesthetic management for children with liver disease include avoidance of medications that are metabolized in the liver (e.g., steroidal neuromuscular blockers) that will have an increased duration of action. All inhaled agents have minimal liver metabolism and reduce hepatic blood flow to a similar extent.

Achalasia

Achalasia[5] is a rare esophageal motor disorder characterized by loss of organized peristalsis in the body of the esophagus, along with elevated lower esophageal sphincter (LES) tone, both of which lead to esophageal stasis. The annual incidence is estimated at 1.6 in 100,000 individuals, with less than 5% of those occurring in children. It is caused by a loss of inhibitory ganglion cells in the myenteric plexus in the esophageal wall. Symptoms include dysphagia for both solids and liquids, chest pain, regurgitation, poor weight gain, and respiratory symptoms such as cough and breathing difficulties, especially when supine. Diagnosis is confirmed by esophagram, which shows a dilated esophagus that tapers at the LES, and by esophageal manometry.

The initial management of achalasia in children includes endoscopy with pneumatic dilation of the LES and is repeated if symptoms recur. Advanced surgical management, after one or more dilations, consists of peroral endoscopic myotomy, or Heller myotomy via laparoscopy.

Induction of anesthesia in these children carries a significant risk of pulmonary aspiration as a result of esophageal stasis and requires strategies to mitigate this risk. Prolonged fasting times may decrease the food burden in the esophagus but do not guarantee an empty esophagus. Awake (or sedated) nasogastric tube placement with esophageal evacuation before induction can further decrease esophageal content. Nebulized lidocaine beforehand can help facilitate this process. Rapid sequence induction should be performed by an experienced laryngoscopist with the head of the bed elevated.

A DEEPER DIVE

Almost all anesthetics for children with GI disease include **esophagogastroduodenoscopy (EGD)** and/or **colonoscopy**. Common pediatric indications for EGD include evaluation of reflux, chronic abdominal pain, periodic biopsies for eosinophilic esophagitis, evaluation and treatment of esophageal varices in chronic liver disease, unexplained weight loss, and diagnosis/evaluation of Crohn disease or ulcerative colitis. Common indications for colonoscopy in children include evaluation of chronic diarrhea, inflammatory bowel disease, and familial polyposis, among others. EGD is performed in the supine or lateral position, depending on the preference of the endoscopist. Colonoscopy is almost always performed in the lateral position, though the supine position is preferred by some.

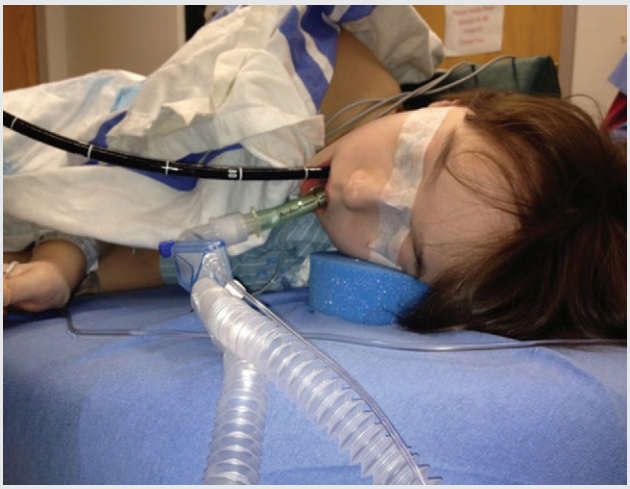
There are a variety of anesthetic techniques for these procedures, and every anesthesia provider (at least at the Children's Hospital of Philadelphia) will tell you that their technique is the best and safest of them all, and the patient is in grave danger if anyone else's technique is used. The techniques discussed assume the patient is an outpatient without IV access. If the child has an IV, propofol is usually used for induction. Let us take a deeper dive into the different anesthetic techniques used for EGD and colonoscopy.

(Continued)

A DEEPER DIVE—cont'd

Esophagogastroduodenoscopy (EGD)

- Many different techniques have been successfully used, including deep sedation with a natural airway, or general anesthesia with a supraglottic airway (SGA) or endotracheal tube.
- The most important consideration is maintenance of upper airway patency during shifting levels of stimulation as the endoscopist maneuvers the scope from mouth to duodenum, and back.
- These procedures tend to end abruptly with little advance warning.
- Some anesthesiologists use the natural airway approach with propofol (bolus and continuous infusion) and monitoring of end-tidal CO_2 via nasal cannula, which also supplies supplemental oxygen. This approach is unappealing because it is difficult to keep the patient motionless with pure propofol and you end up toggling between calm, and apneic with a lot of chin lifts, jaw thrusts, and transient hypoxemia. Remember, the apneic dose of propofol is lower than the analgesic dose.
- Some anesthesiologists try intermittent face mask airway with sevoflurane, but if the procedure is prolonged, the sevoflurane will inevitably escape into the room. If the endoscopist is quite skilled, however, one could anesthetize the child with sevoflurane at a high level, and then turn it off completely when the procedure begins, and the procedure will be done before the sevoflurane has worn off.
- The most perfect anesthetic technique for EGD is the SGA/sevoflurane method. The child is induced with sevoflurane, and an SGA is inserted when an appropriate level of unconsciousness is achieved (Fig. 6.1). Occasionally, a small bolus of propofol is needed for teenagers. Ondansetron is administered as prophylaxis for postoperative nausea and vomiting PONV. The child breathes spontaneously throughout the procedure and the SGA is removed along with the endoscope. The child is then ready for discharge about 15 to 20 minutes later, nausea-free.
- Opioids are rarely used because pain is not a prominent concern during and after upper endoscopy, and their administration may delay awakening and contribute to the usual opioid side effects.
- Tracheal intubation is occasionally preferred for EGD because of an underlying condition that puts the patient at risk for pulmonary aspiration, such as achalasia, severe reflux, or ablation of esophageal varices, which carries the possibility of significant bleeding.



• **Fig 6.1.** Laryngeal mask anesthesia for upper endoscopy. (Photo credit to Petar Mamula)

Colonoscopy

- Most children require extensive fasting and bowel cleansing before colonoscopy, and we have found a small incidence of hypoglycemia upon admission to the endoscopy unit. For this reason, finger stick glucose determinations are performed on all children after induction of general anesthesia.
- Colonoscopy can often be stimulating because there may be numerous twists and turns of the colonoscope to reach the cecum.
- These children do not require tracheal intubation unless they are susceptible to pulmonary aspiration of gastric contents because of a preexisting medical condition.
- After induction of general anesthesia with sevoflurane, as for EGD, a sevoflurane-based technique with an SGA is the preferred technique; however, a propofol-based anesthetic technique with a natural airway and nasal cannula is a reasonable alternative.

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